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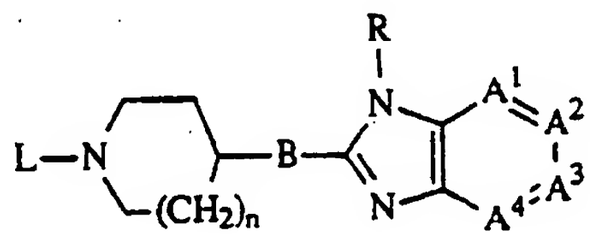
(54) Title: NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED PYRIDINYL DERIVATIVES



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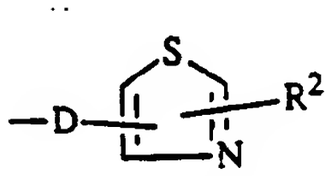

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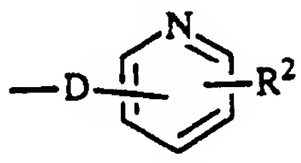

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(57) Abstract

Substituted thiazolyl and substituted pyridinyl derivatives of formula (I), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula $-CH=CH-CH=CH-$ (a-1), $-N=CH-CH=CH-$ (a-2), $-CH=N-CH=CH-$ (a-3), $-CH=CH-N=CH-$ (a-4), $-CH=CH-CH=N-$ (a-5), $-N=CH-N=CH-$ (a-6) or $-CH=N-CH=N-$ (a-7); B represents NR^1, CH_2, O, S, SO or SO_2 wherein R^1 is hydrogen or C_{1-4}alkyl; R is a radical of formula (b-1) or (b-2); wherein D is C_{1-4}alkanediyl; R^2 is C_{1-6}alkyl; n is 0, 1 r 2; L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; aryl C_{1-6}alkyloxycarbonyl; or a radical of formula -Alk-R^3 (c-1); -Alk-Y-R^4 (c-2); -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); or $-CH_2-CHOH-CH_2-O-R^6$ (c-4); have antiallergic properties. Compositions containing the same and methods of treating warm-blooded animals suffering from allergic diseases.

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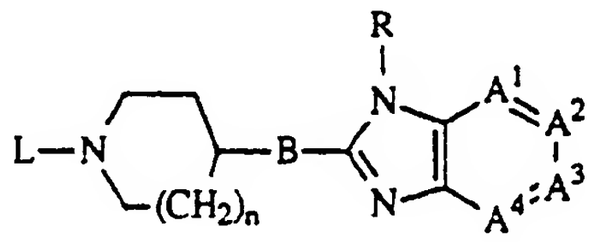
NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED PYRIDINYL DERIVATIVES

Background of the invention

In US-4,556,660; 4,634,704; 4,695,569; 4,695,575; 4,588,722; 4,835,161; 4,897,401 and in EP-A-0,206,415 and 0,297,661 there are disclosed benzimidazole and imidazopyridine substituted piperidine derivatives as antihistaminics and serotonin antagonists.

Description of the invention:

The present invention is concerned with novel substituted thiazolyl and substituted pyridinyl derivatives having the formula :



(I),

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=CH-CH=CH- (a-1),

-N=CH-CH=CH- (a-2),

-CH=N-CH=CH- (a-3),

-CH=CH-N=CH- (a-4),

-CH=CH-CH=N- (a-5),

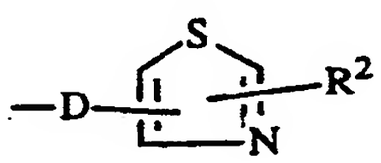
-N=CH-N=CH- (a-6) or

-CH=N-CH=N- (a-7);

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy or trifluoromethyl;

B represents NR^1, CH_2, O, S, SO or SO_2 wherein R^1 is hydrogen or C_{1-4}alkyl;

R is a radical of formula;



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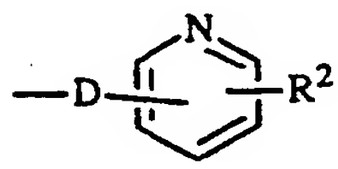
or



(b-2)

;

wherein D is C_{1-4}alkanediyl;

R^2 is C_{1-6}alkyl;

n is 0, 1 or 2 ;

L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; or a radical of formula

-Alk-R^3	(c-1);
-Alk-Y-R^4	(c-2);
-Alk-Z^1-C(=X)-Z^2-R^5	(c-3); or
-CH_2-CHOH-CH_2-O-R^6	(c-4); wherein

R^3 is cyano, aryl or Het;

R^4 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^5 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^6 is aryl or naphthalenyl;

Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;

Z^1 and Z^2 each independently are O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;

X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;

each Alk independently is C_{1-6}alkanediyl;

each Het is :

(i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;

(ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or

(iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;

wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy, mercapto, hydroxyC_{1-6}alkyl, C_{1-6}alkyl-carbonyloxy, aryl, arylC_{1-6}alkyl, carboxyl, C_{1-6}alkylaminocarbonylamino, aryl-aminocarbonylamino, oxo or thio;

each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl.

In the compounds of formula (I) where R^3, R^4 or R^5 is Het, said Het may be partly or completely saturated, or unsaturated. The compounds of formula (I) wherein Het is partly saturated or unsaturated and is substituted with hydroxy, mercapto or amino, may also exist in their tautomeric forms. Such forms although not explicitly indicated herein-above, are intended to be included within the scope of the invention.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methyl-ethyl, butyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl; C_{1-6}alkyl defines C_{1-4}alkyl radicals as defined hereinabove and the higher homologs thereof having 5 or 6 carbon atoms; C_{1-12}alkyl defines C_{1-4}alkyl radicals as defined hereinabove and the higher homologs thereof having from 5 to 12 carbon atoms; C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C_{3-6}alkenyl defines straight and

branch chained hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; and when a C_{3-6}alkenyl is substituted on a heteroatom, then the carbon atom of said C_{3-6}alkenyl connected to said heteroatom preferably is saturated; C_{1-4}alkanediyl defines bivalent straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the branched isomers thereof; C_{1-6}alkanediyl defines C_{1-4}alkanediyl radicals as defined hereinabove and the higher homologs thereof having 5 or 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. Said salt forms can conveniently be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term acid addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be indicated by the stereochemical descriptors R and S.

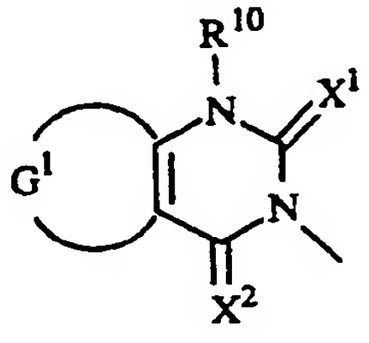
Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like; and enantiomers may be separated from each other following art-known resolution methods, for example, by the selective crystallization of their diastereomeric salts with chiral

acids. Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reactions occur stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective methods of preparation. These methods will advantageously employ enantiomerically pure starting materials. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

In particular, the radical Het as defined hereinabove may be selected from pyridinyl, optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, hydroxy, C_{1-6}alkylcarbonyloxy, arylC_{1-6}alkyl and carboxyl; pyridinyloxide, optionally substituted with nitro; pyrimidinyl, optionally substituted with one or two substituents each independently selected from halo, amino, C_{1-6}alkylamino, arylC_{1-6}alkylamino, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio and arylC_{1-6}alkyl; pyridazinyl, optionally substituted with C_{1-6}alkyl or halo; pyrazinyl, optionally substituted with halo, amino or C_{1-6}alkyl; thienyl, optionally substituted with halo or C_{1-6}alkyl; furanyl, optionally substituted with halo or C_{1-6}alkyl; pyrrolyl, optionally substituted with C_{1-6}alkyl; thiazolyl, optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl or arylC_{1-6}alkyl; imidazolyl, optionally substituted with one or two substituents each independently selected from C_{1-6}alkyl, arylC_{1-6}alkyl and nitro; tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,3,4-thiadiazolyl, optionally substituted with C_{1-6}alkyl or amino; 5,6-dihydro-4H-1,3-thiazin-2-yl, optionally substituted with C_{1-6}alkyl; 4,5-dihydrothiazolyl, optionally substituted with C_{1-6}alkyl; oxazolyl, optionally substituted with C_{1-6}alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl, optionally substituted with C_{1-6}alkyl; 3,4-dihydro-4-oxopyrimidinyl or 4,5-dihydro-4-oxopyrimidinyl, both radicals optionally substituted with up to 3 substituents selected from C_{1-6}alkyl, amino, C_{1-6}alkylaminocarbonylamino, arylaminocarbonylamino, arylC_{1-6}alkylamino and C_{1-6}alkylamino; 2,3-dihydro-3-oxopyridazinyl; 2-oxo-3-oxazolidinyl; pyrrolidinyl; piperidinyl; morpholinyl; thiomorpholinyl; dioxanyl, optionally substituted with C_{1-6}alkyl; indolyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinolinyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinazolinyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinoxalinyl, optionally substituted with C_{1-6}alkyl; phthalazinyl, optionally substituted with halo; 1,3-dioxo-1H-isoindol-2(3H)-yl; 2,3-dihydro-3-oxo-4H-benzoxazinyl and 2,3-dihydro-1,4-benzodioxinyl, both being optionally

substituted with C_{1-6}alkyl or halo; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzopyranyl, both being optionally substituted with C_{1-6}alkyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, optionally substituted with C_{1-6}alkyl; 6-purinyl, and

a bicyclic heterocyclic radical of formula



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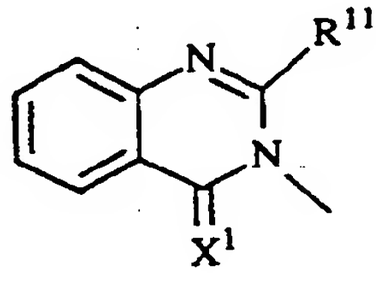

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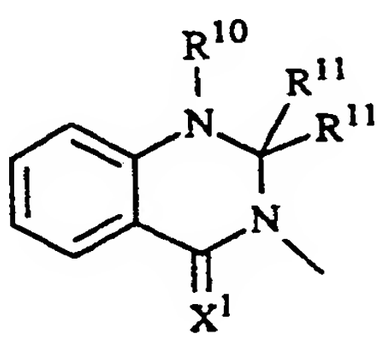

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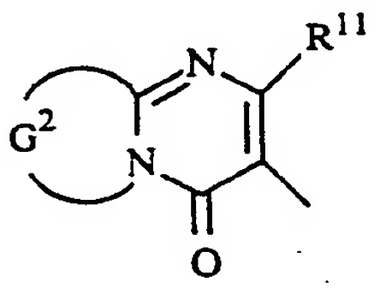

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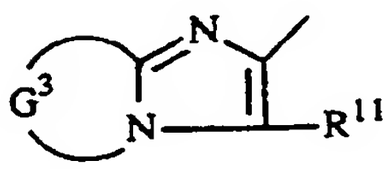

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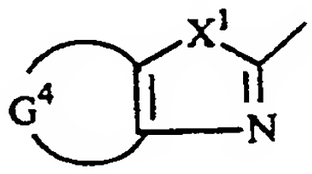

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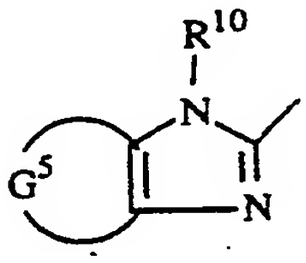

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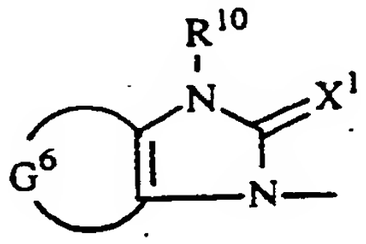


(d-8),

wherein

X^1 and X^2 each independently are O or S ;

each R^{10} independently is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxycarbonyl;

each R^{11} independently is hydrogen, C_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, halo or C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;

G^1 is -CH=CH-CH=CH-; -S-CH=CH- or -N=CH-NH- ;

G^2 is -CH=CH-CH=CH-, $-(CH_2)_4$-, -S-$(CH_2)_2$-, -S-$(CH_2)_3$-, -S-CH=CH-, -CH=CH-O-, -NH-$(CH_2)_2$-, -NH-$(CH_2)_3$-, -NH-CH=CH-, -NH-N=CH-CH_2-, -NH-CH=N- or -NH-N=CH- ;

G^3 is -CH=CH-CH=CH-, $-CH_2-NH-(CH_2)_2-$, -S-CH=CH-, $-S-(CH_2)_3-$, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

G^4 is -CH=CH-CH=CH-, $-CH_2-NH-(CH_2)_2-$, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N-;

G^5 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

G^6 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

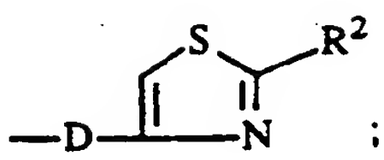
wherein one or two hydrogen atoms in the benzene part of the radicals of formula (d-2) or (d-3) or one or two hydrogen atoms in said radicals G^1, G^2, G^3, G^4, G^5 or G^6 may be replaced by C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxy or halo, when connected to a carbon atom; or by C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl or arylC_{1-6}alkyl when connected to a nitrogen atom; and aryl is as defined hereinabove.

Aryl as used in the definition of R^3, R^4 and R^5, in particular is phenyl optionally substituted with halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy; aryl as used in the definition of R^6 in particular is phenyl optionally substituted with halo.

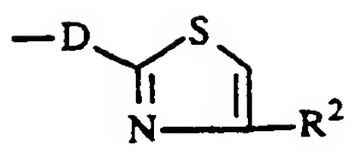
A particular subgroup among the compounds of formula (I) comprises those compounds of formula (I) wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical of formula (a-1) or (a-2); another particular subgroup among the compounds of formula (I) comprises those compounds of formula (I) wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical having a formula (a-3) through (a-5); wherein one or two hydrogen atoms in said radicals (a-1) to (a-5) may each independently be replaced by C_{1-6}alkyloxy or hydroxy.

Particularly interesting compounds are those compounds of any of the former groups or subgroups wherein B is NR^2, O or CH_2; and/or L is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, or a radical of formula (c-1), (c-2), (c-3) or (c-4).

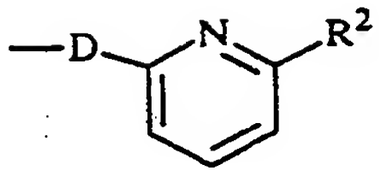
More particularly interesting compounds are those particularly interesting compounds of formula (I) wherein B is NH or CH_2; and/or n is 1 or 2; and/or R is a radical of formula :



(b-1-a)



(b-1-b)



(b-2-a)

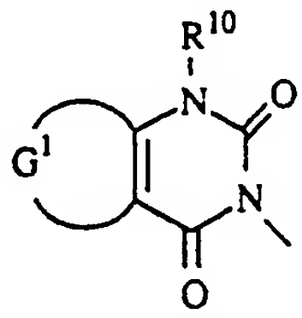
Preferred compounds are any of the above defined groups of compounds wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); wherein one or two hydrogen atoms in said radicals (a-1) or (a-2) may each independently be replaced by C_{1-6}alkyloxy or hydroxy; D is CH_2; and/or L is hydrogen; C_{1-6}alkyl; a radical of formula (c-1) wherein R^3 is aryl or Het; a radical of formula (c-2) wherein Y is NH or O and R^4 is aryl or Het; or a radical of formula -Alk-NH-CO-Het (c-3-a); wherein each Het is pyridinyl, optionally substituted with amino or C_{1-6}alkyl; pyrimidinyl, optionally substituted with amino or C_{1-6}alkyl; pyrazinyl, optionally substituted with amino; thienyl; furanyl; thiazolyl, optionally substituted with C_{1-6}alkyl; imidazolyl, optionally substituted with C_{1-6}alkyl; tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,3,4-thiadiazolyl, optionally substituted with C_{1-6}alkyl or amino; oxazolyl, optionally substituted with C_{1-6}alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl; 3,4-dihydro-4-oxopyrimidinyl optionally substituted with up to 3 substituents selected from C_{1-6}alkyl, amino and C_{1-6}alkylamino; 2-oxo-3-oxazolidinyl; indolyl, optionally substituted with C_{1-6}alkyl; phthalazinyl; 2-oxo-2H-1-benzopyranyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, optionally substituted with C_{1-6}alkyl; 6-purinyl, or a bicyclic heterocyclic radical of formula (d-1) to (d-8) as defined hereinabove, wherein R^{10} and R^{11} each independently are hydrogen or C_{1-6}alkyl and in the radicals (d-2) and (d-3), X^1 is O, and;

each aryl is unsubstituted phenyl; phenyl substituted with 1 or 2 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl and C_{1-6}alkyloxy; and optionally further substituted with a third substituent selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy.

More preferred compounds are those preferred compounds wherein L is hydrogen or C_{1-3}alkyl.

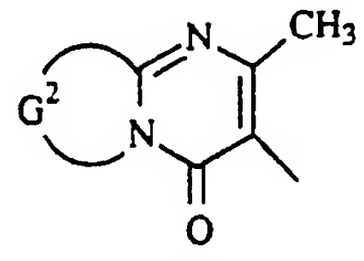
Further more preferred compounds are those preferred compounds wherein L is a radical of formula -Alk-R^3 (c-1) wherein R^3 is 4-methoxyphenyl; 4-hydroxyphenyl; thienyl; thiazolyl optionally substituted with C_{1-6}alkyl; oxazolyl; 4,5-dihydro-1H-tetrazolyl optionally substituted with C_{1-6}alkyl; 2,3-dihydro-2-oxo-benzimidazol-1-yl;

1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl; thienyl; 2-oxo-2H-1-benzopyranyl or R^3 is a radical of formula



(d-1-a)

or

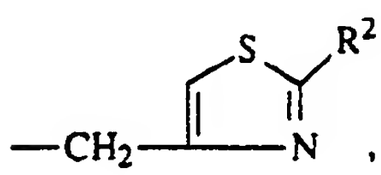


(d-4-a)

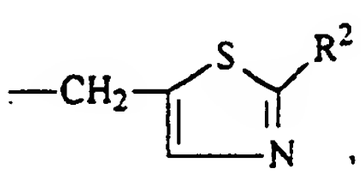
wherein G^1, G^2 and R^{10} are as defined hereinabove.

Still other more preferred compounds are those preferred compounds wherein L is a radical of formula -Alk-Y-R^4 (c-2) wherein Y is NH or O and R^4 is thiazolyl, pyridinyl, 1,3,4-thiadiazolyl optionally substituted with C_{1-6}alkyl or amino, pyrimidinyl optionally substituted with amino, 6-purinyl, 3,4-dihydro-4-oxopyrimidinyl, phthalazinyl or 3H-imidazo[4,5-c]pyridin-2-yl.

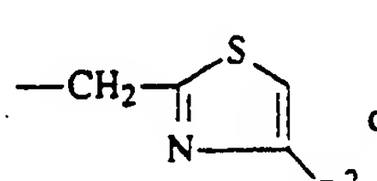
Interesting compounds within the present invention are those compounds of formula (I) wherein -A^1=A^2-A^3=A^4- represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH_2 or O; R represents a radical of formula



(b-1-c)

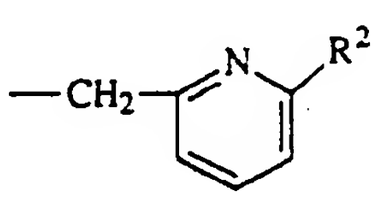


(b-1-d)



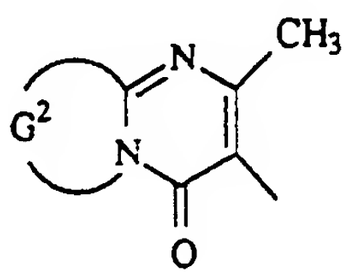
(b-1-e)

or



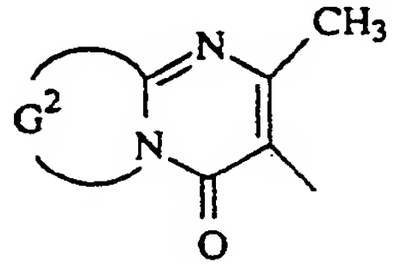
(b-2-b)

R^2 represents C_{1-4}alkyl; n is 1; L represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{1-4}alkanediyl; R^3 represents phenyl, C_{1-4}alkyloxyphenyl or a radical of formula



wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-; Y represents O or NH; R^4 represents hydrogen, C_{1-4}alkyl or pyrimidinyl; R^5 represents C_{1-4}alkyl; Z^1 represents NH; Z^2 represents O; and X represents O.

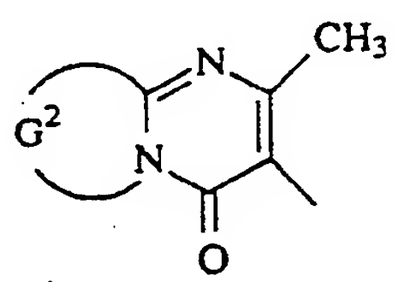
Particularly interesting compounds are those interesting compounds wherein B represents NH or CH_2; R^2 represents methyl; L represents C_{1-4}alkyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{2-4}alkanediyl; R^3 represents 4-methoxyphenyl or a radical of formula



wherein G^2 represents CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-; Y represents O or NH; and R^4 represents C_{1-4}alkyl or 2-pyrimidinyl.

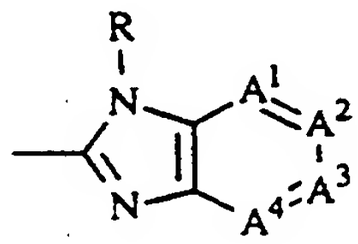
Other particularly interesting compounds are those interesting compounds wherein B represents NH or CH_2; R^2 represents methyl; L represents hydrogen, C_{1-4}alkyloxycarbonyl, phenylmethyl, hydroxyethyl or aminoethyl.

Especially interesting compounds are those particularly interesting compounds wherein L represents methyl or a radical of formula -Alk-R^3 (c-1), Alk represents 1,2-ethanediyl and R^3 represents 4-methoxyphenyl or a radical of formula



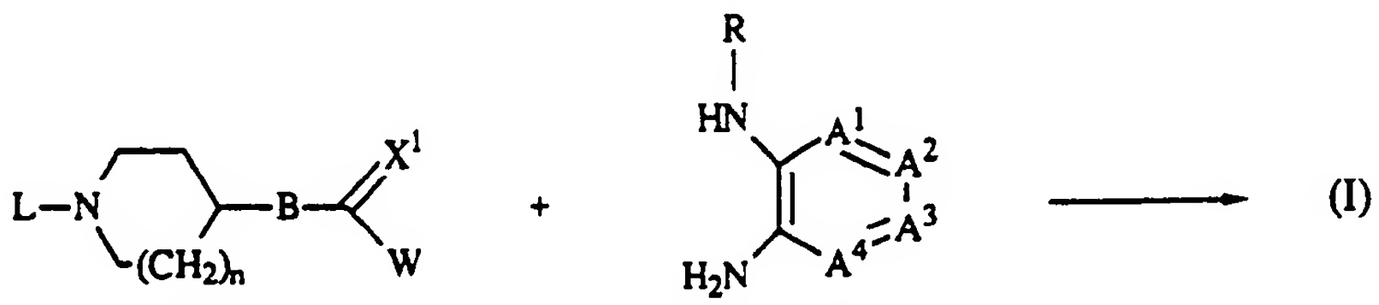
wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-.

In order to simplify the structural representation of some of the compounds and intermediates in the following preparations the moiety containing the imidazole group fused to a benzene, pyridine or pyrimidine ring will hereinafter be represented by the symbol Q.



= -Q

The compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) with an appropriately substituted diamine of formula (III).

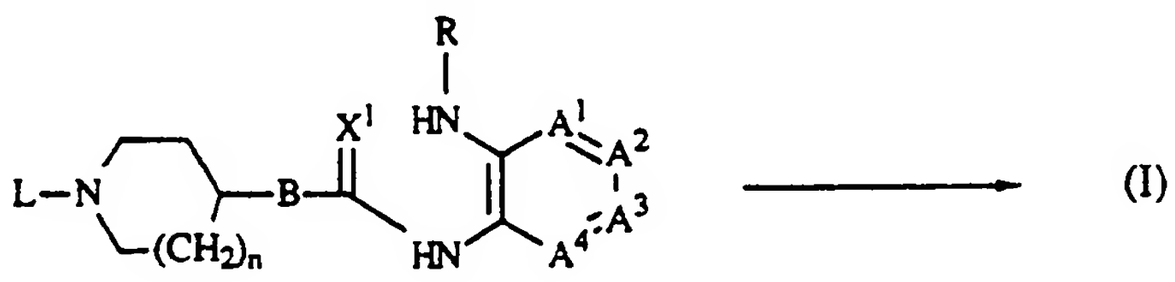


(II) (III) (I)

In this and the following reaction schemes W represents an appropriate reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo; C_{1-6}alkyloxy; C_{1-6}alkylthio, aryloxy or arylthio; and X^1 denotes O, S or NH.

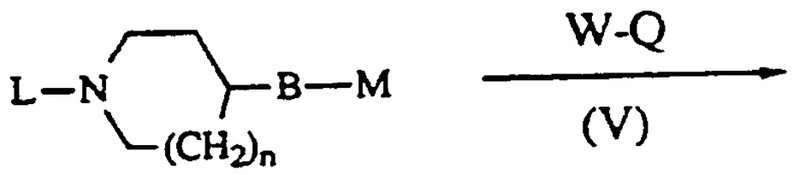
The derivatives of formula (II) wherein B is CH_2 and W is halo may be generated in situ, for example, by halogenating the corresponding carboxylic acid with thionyl chloride, phosphorous trichloride, phosphoryl chloride, polyphosphoric acid and the like reagents. The reaction of (II) with (III) may be conducted in a suitable reaction-inert solvent such as, for example, a hydrocarbon, e.g., benzene, hexane and the like; an ether, e.g., 1,1'-oxybisethane, tetrahydrofuran and the like; a ketone, e.g., 2-propanone, 2-butanone and the like; an alcohol, e.g., methanol, ethanol, 2-propanol, 1-butanol and the like; a halogenated hydrocarbon, e.g., trichloromethane, dichloromethane and the like; an organic acid, e.g., acetic acid, propanoic acid and the like; a dipolar aprotic solvent e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; or a mixture of such solvents. Depending upon the nature of the solvent and W it may be appropriate to add to the reaction mixture a base such as is commonly employed in the art of conducting N-alkylation reactions and/or a iodide salt such as an alkali metal iodide. Elevated temperatures and stirring may enhance the reaction rate.

In some instances the reaction of (II) with (III) may first yield an intermediate of formula (II-a) which subsequently may be cyclized to the desired compound of formula (I), either in situ or, if desired, after isolation and purification.

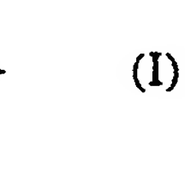


(II-a) (I)

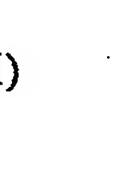
The compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (V) following art-known substitution reaction procedures. In (IV) and hereinafter, M is hydrogen when B is other than CH_2, or M represents an alkali or earth alkaline metal such as, for example, lithium or magnesium, when B represents CH_2.



(IV)

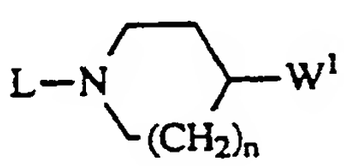


(V)

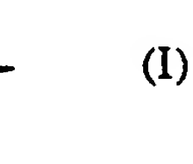


(I)

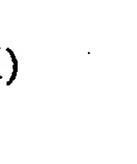
Similarly, the compounds of formula (I) can also be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (VII) wherein M has the previously defined meaning. In formula (VI) and hereinafter W^1 represents an appropriate leaving group such as, for example, halo, e.g., chloro, bromo and the like; or a sulfonyloxy group such as, for example, methanesulfonyloxy, 4-methylbenzenesulfonyloxy and the like.



(VI)

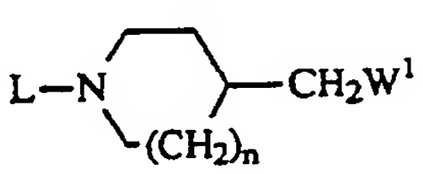


(VII)

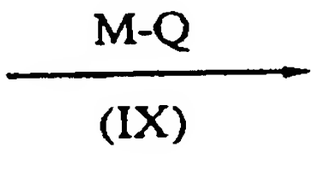


(I)

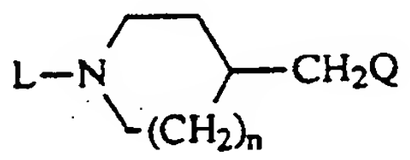
The compounds of formula (I) wherein B is $-CH_2-$, said compounds being represented by formula (I-a), can also be prepared by reacting an intermediate of formula (VIII) with an intermediate of formula (IX) or alternatively, by reacting an intermediate of formula (X) with an intermediate of formula (XI).



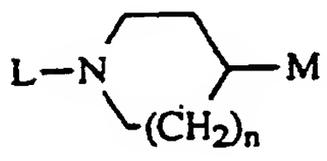
(VIII)



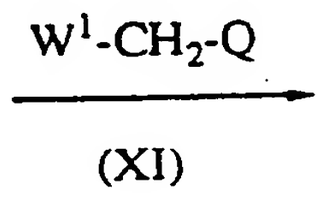
(IX)



(I-a)



(X)

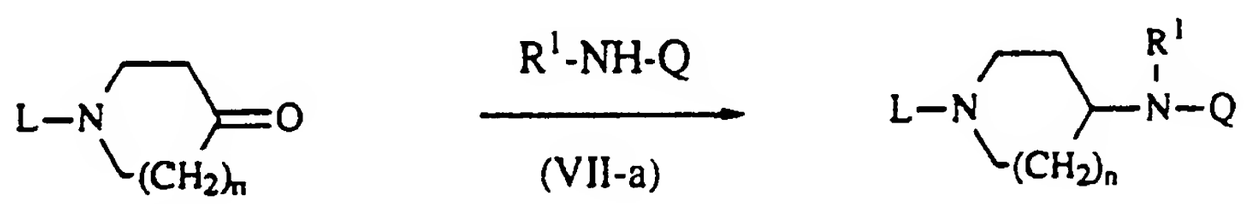


(XI)

The reactions of (IV), (VI) , (VIII) and (X) with respectively (V), (VII), (IX) and (XI) may conveniently be conducted in an appropriate reaction-inert solvent such as for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene and the like; an ether,

e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; a halogenated hydrocarbon, e.g. trichloromethane and the like; N,N-dimethylformamide; N,N-dimethylacetamide; nitrobenzene; dimethylsulfoxide; 1-methyl-2-pyrrolidinone and the like; and when M is hydrogen, said solvent may also be a C_{1-6}alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like. In some instances, particularly when B is a heteroatom, the addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, e.g., sodium carbonate, sodium hydrogen carbonate and the like; sodium hydride; or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine and/or the addition of an iodide salt, preferably an alkali metal iodide, may be appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. A convenient alternative for reacting the intermediate of formula (IV) wherein -B-M represents $-NH_2$ with the reagents of formula (V) comprises stirring and heating the reactants in the presence of copper metal in a reaction-inert solvent such as described hereinbefore, in particular a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide and the like.

The compounds of formula (I) wherein B is $-NR^1-$, said compounds being represented by formula (I-b), can also be prepared by reacting an intermediate of formula (XII) with an intermediate of formula (VII) wherein B-M represents a radical $-NR^1-H$, said intermediate being represented by formula (VII-a), following art-known reductive N-alkylation procedures.



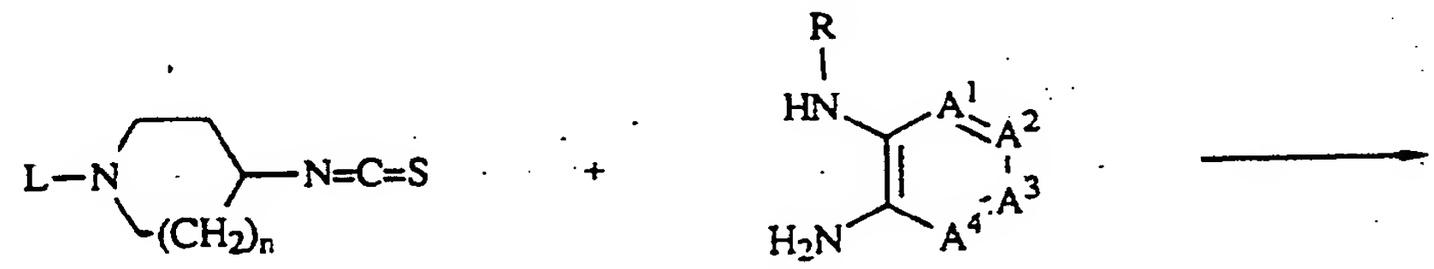
(XII) (I-b)

The reaction of (XII) with (VII-a) can conveniently be carried out by mixing the reactants in a suitable reaction-inert solvent with an appropriate reductant. Preferably, the ketone of formula (XII) is first reacted with the intermediate of formula (VII-a) to form an enamine, which optionally may be isolated and further purified, and subsequently reducing said enamine. Suitable solvents are, for example, water; C_{1-6}alkanols, e.g., methanol, ethanol, 2-propanol and the like; ethers, e.g., 1,4-dioxane and the like; halogenated hydrocarbons, e.g., trichloromethane and the like; dipolar aprotic solvents, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide and the like; or a mixture of such solvents. Appropriate reductants are for example, metal or complex metal hydrides, e.g., sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride and the like. Alternatively, hydrogen in

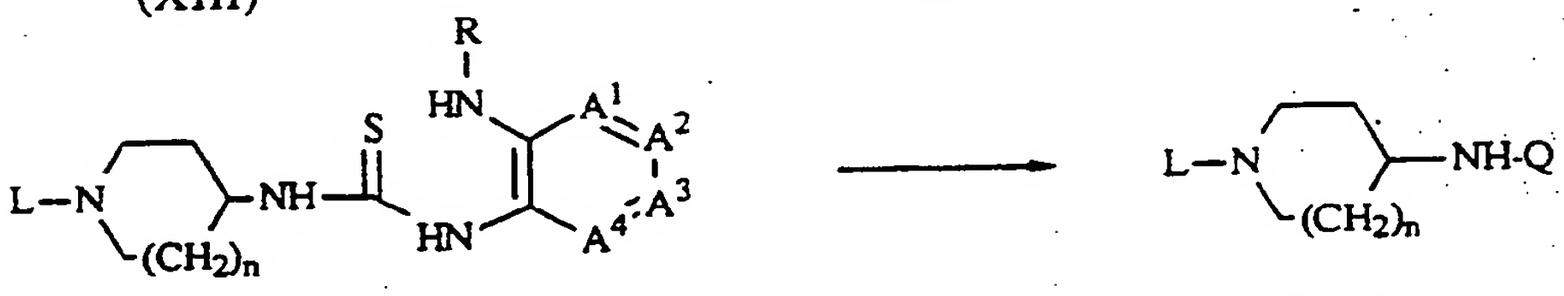
the presence of a suitable catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like may be used as reductant. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products it may be advantageous to add an appropriate catalyst poison to the reaction mixture such as, for example, thiophene and the like.

The compounds of formula (I-b) wherein R^1 is H, said compounds being represented by formula (I-b-1), can also be prepared by a cyclodesulfurization reaction of an appropriate thiourea of formula (II-a) wherein X^1 is S, said thiourea being represented by formula (II-a-1), which may be formed in situ by condensing an isothiocyanate of formula (XIII) with a diamine of formula (III).

Said cyclodesulfurization reaction may be carried out by reacting (II-a-1) with an appropriate alkyl halide, preferably iodomethane, in a suitable reaction-inert organic solvent such as a C_{1-6}alkanol, e.g., methanol, ethanol, 2-propanol and the like. Alternatively, said cyclodesulfurization reaction may also be carried out by the reaction of (II-a-1) with an appropriate metal oxide or salt such as, for example, a Hg(II) or Pb(II) oxide or salt, e.g., HgO, $HgCl_2$, $Hg(OAc)_2$, PbO or $Pb(OAc)_2$ in an appropriate solvent following art-known procedures. In some instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. Also methanediimides, especially dicyclohexylcarbodiimide may be used as cyclodesulfurizing agents.

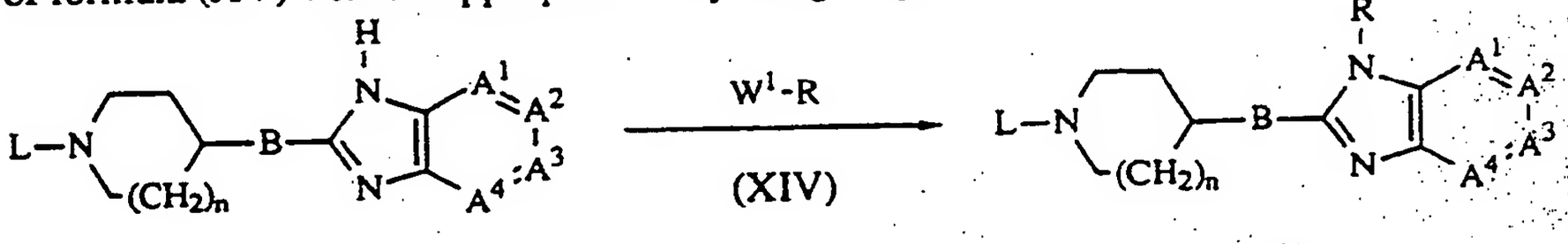


(XIII) (III)



(II-a-1) (I-b-1)

The compounds of formula (I) can also be prepared by N-alkylating an intermediate of formula (XV) with an appropriate alkylating reagent of formula (XIV).

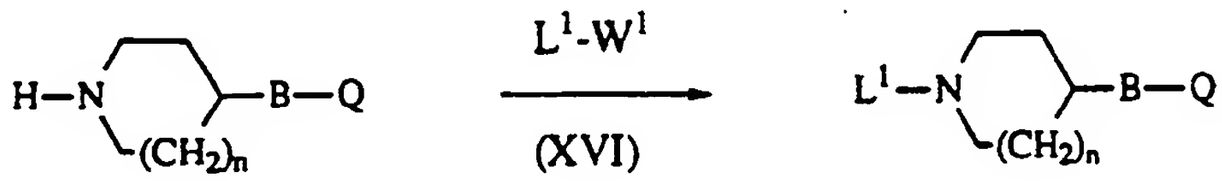


(XV) (XIV) (I)

Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, water; an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Additionally, it may be advantageous to conduct said N-alkylation under an inert atmosphere such as, for example, oxygen-free argon or nitrogen.

Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants with an appropriate base and optionally under an inert atmosphere as described hereinabove, in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylmethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylphosphonium halide, hydroxide, hydrogen sulfate and the like catalysts.

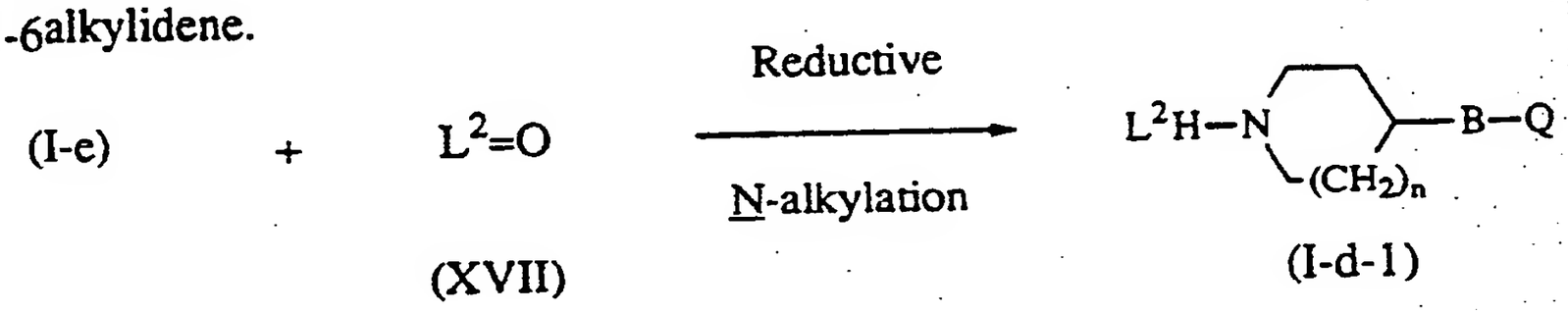
The compounds of formula (I) wherein L is other than hydrogen, said L being represented by L^1, and said compounds being represented by formula (I-d) can also be prepared by N-alkylating a compound of formula (I) wherein L is hydrogen, said compound being represented by (I-e), with an alkylating reagent of formula (XVI).



(I-e) (I-d)

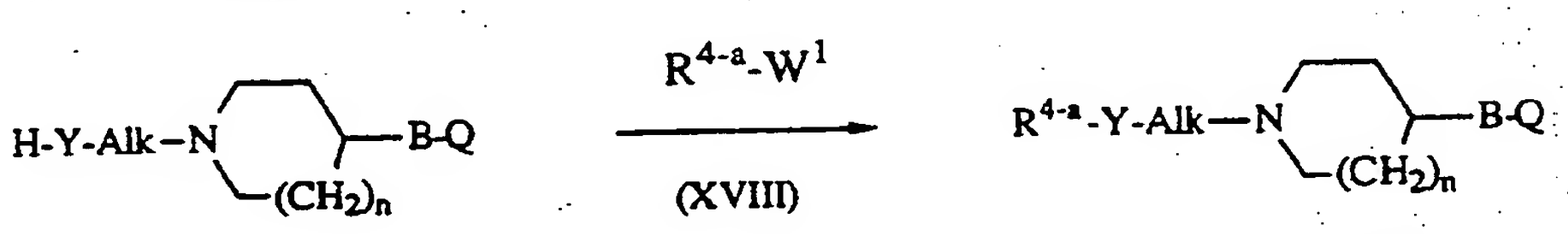
Said N-alkylation is conveniently conducted following art-known N-alkylation procedures as described hereinabove for the preparation of (I) from (XIV) and (XV).

The compounds of formula (I-d) wherein L is C_{3-6}cycloalkyl, C_{1-12}alkyl, a radical of formula (c-1), (c-2) or (c-3), said radicals being represented by the radical L^2H- and said compounds by formula (I-d-1) can also be prepared by the reductive N-alkylation reaction of (I-e) with an appropriate ketone or aldehyde of formula L^2=O (XVII), said L^2=O being an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms are replaced by =O, and L^2 is a geminal bivalent radical comprising C_{3-6}cycloalkylidene, C_{1-12}alkylidene, R^3-C_{1-6}alkylidene, R^4-Y-C_{1-6}alkylidene and R^5-Z^2-C(=X)-Z^1-C_{1-6}alkylidene.

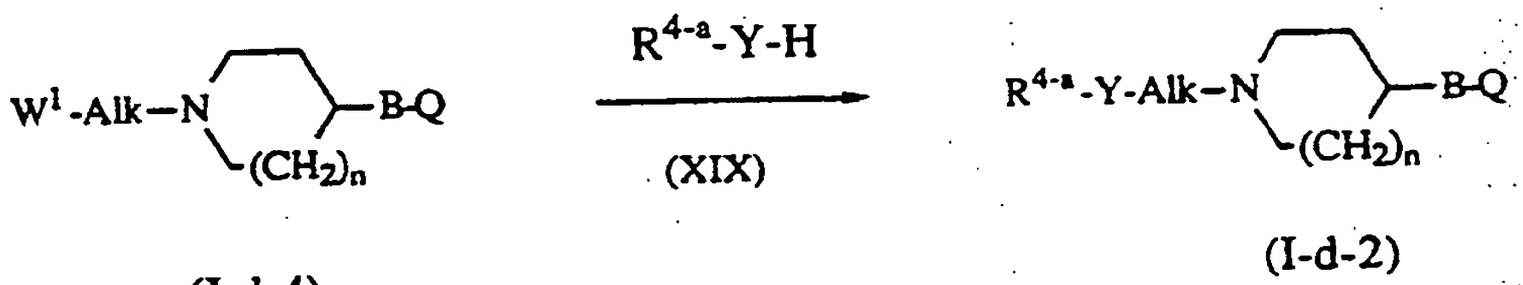


Said reductive N-alkylation can conveniently be carried out following the procedures described hereinabove for the preparation of compounds of formula (I-b) from (VII-a) and (XII), more particularly following the catalytic hydrogenation procedures.

The compounds of formula (I) wherein L is a radical of formula (c-2) and R^4 is aryl or Het, said R^4 being represented by R^{4-a} and said compounds by formula (I-d-2) may also be prepared by alkylating a compound of formula (I) wherein L is a radical of formula (c-2) and R^4 is hydrogen, said compounds being represented by formula (I-d-3), with a reagent of formula (XVIII).

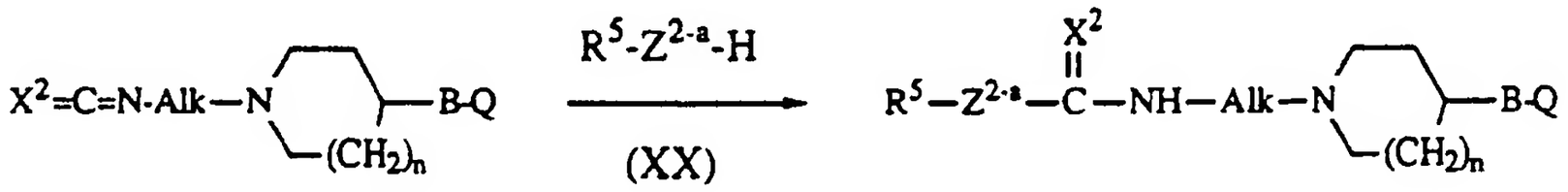


Similarly, the compounds of formula (I-d-2) may also be prepared by treating a compound of formula (I-d-4) with a reagent of formula (XIX).



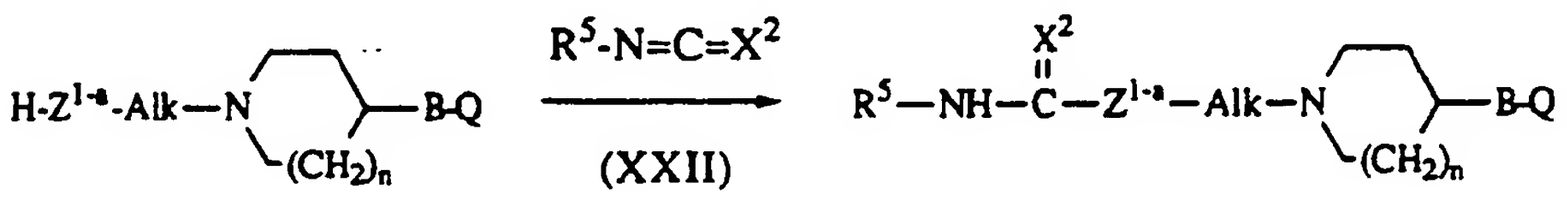
The alkylation reactions of (I-d-3) with (XVIII) and (I-d-4) with (XIX) may conveniently be conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; and a dipolar aprotic solvent, e.g., N,N-dimethylformamide; N,N-dimethylacetamide; dimethyl sulfoxide; nitrobenzene; 1-methyl-2-pyrrolidinone; and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I) wherein L is a radical of formula (c-3), Z^1 is NH, Z^2 is other than a direct bond and X is other than NR^9, said Z^2 and X being represented by Z^{2-a} and X^2, and said compounds by (I-d-5), can be prepared by reacting an isocyanate ($X^2 = O$) or isothiocyanate ($X^2 = S$) of formula (XXI) with a reagent of formula (XX).



(XXI) (XX) (I-d-5)

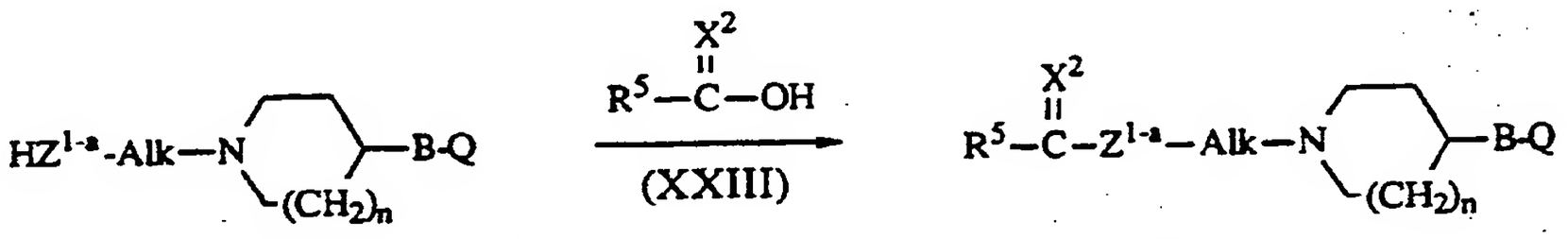
The compounds of formula (I) wherein L is a radical of formula (c-3), Z^2 is NH, Z^1 is other than a direct bond and X is other than NR^9, said Z^1 and X being represented by Z^{1-a} and X^2, and said compounds by (I-d-6), can be prepared by reacting an isocyanate ($X^2 = O$) or isothiocyanate ($X^2 = S$) of formula (XXII) with a compound of formula (I-d-7).



(I-d-7) (XXII) (I-d-6)

The reaction of (XX) with (XXI), or (XXII) with (I-d-7) can generally be conducted in a suitable reaction-inert solvent such as, for example, an ether, e.g., tetrahydrofuran and the like, a halogenated hydrocarbon, e.g., trichloromethane and the like. Elevated temperatures may be suitable to enhance the rate of the reaction.

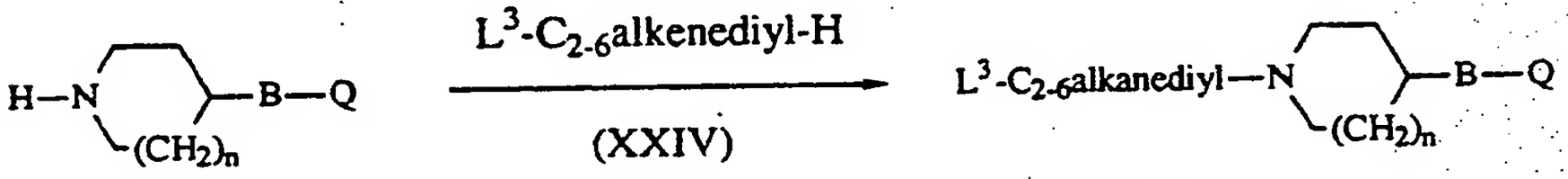
The compounds of formula (I) wherein L is a radical of formula (c-3), Z^2 is a direct bond, Z^1 is other than a direct bond and X is other than NR^9, said Z^1 and X being represented by Z^{1-a} and X^2, said compounds being represented by (I-d-8), can be prepared by reacting a reagent of formula (XXIII) or a reactive functional derivative thereof with a compound of formula (I-d-7).



(I-d-7) (XXIII) (I-d-8)

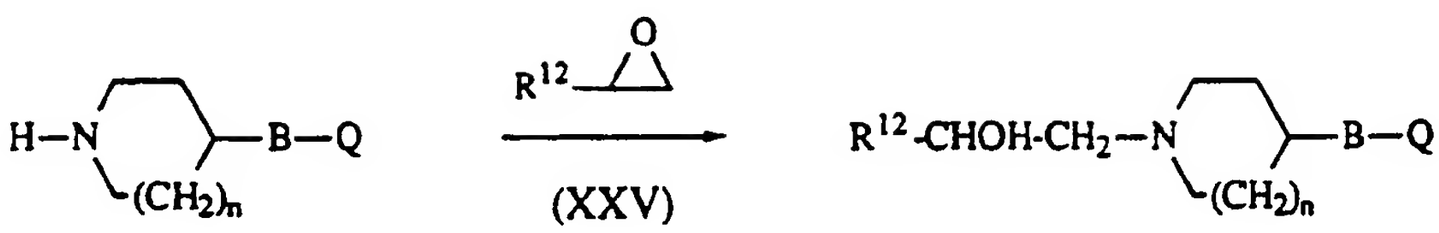
The reaction of (XXIII) with (I-d-7) may generally be conducted following art-known esterification or amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g., an anhydride or a carboxylic acid halide, which subsequently is reacted with (I-d-7); or by reacting (XXIII) and (I-d-7) with a suitable reagent capable of forming amides or esters, e.g., N,N-methanetetraylbis[cyclohexamine], 2-chloro-1-methylpyridinium iodide and the like. Said reactions may most conveniently be conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like. The addition of a base such as, for example, N,N-diethylethanamine and the like may be appropriate.

The compounds of formula (I) wherein L is a radical of formula L^3-C_{2-6}alkanediyl, said L^3 being aryl, Het or a radical of formula R^5-Z^2-C(=X)-, and said compounds being represented by formula (I-d-9), may also be prepared by the addition reaction of a compound of formula (I-e) to an appropriate alkene of formula (XXIV).



(I-e) (XXIV) (I-d-9)

The compounds of formula (I) wherein L is 2-hydroxy-C_{2-6}alkyl or a radical of formula (c-4), said compounds being represented by formula (I-d-10), can be prepared by reacting a compound of formula (I-e) with an epoxide (XXV) wherein R^{12} is hydrogen, C_{1-4}alkyl or a radical R^6-O-CH_2-.



(I-e) (XXV) (I-d-10)

The reaction of (I-e) with respectively (XXIV) and (XXV) may be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for example, a ketone, e.g., 2-propanone, 4-methyl-2-pentanone, an ether, e.g., tetrahydrofuran, 1,1'-oxybisethane, an alcohol, e.g., methanol, ethanol, 1-butanol, a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, and the like.

The compounds of formula (I) wherein R^3, R^4 or R^5 are Het, may also be prepared following art-known procedures for preparing heterocyclic ring systems or following analogous methods. A number of such cyclization procedures are described in for example, US-4,695,575 and in the references cited therein, in particular US-4,335,127; 4,342,870 and 4,443,451.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation. Some examples of such procedures are cited hereinafter. The compounds of formula (I) containing a cyano substituent can be converted into the corresponding amines by stirring and, if desired, heating the starting cyano compounds in a hydrogen containing medium in the presence of an appropriate catalyst such as, for example, platinum-on-charcoal, Raney-nickel and the like catalysts. Suitable solvents are, for example, methanol, ethanol and the like. Amino groups may be alkylated or acylated following art-known procedures such as, for example, N-alkylation, N-acylation, reductive N-alkylation and the like methods. The compounds of formula (I) containing an amino group substituted with a radical arylmethyl, may be hydrogenolyzed by treating the starting compound with hydrogen in the presence of a suitable catalyst, e.g., palladium-on-charcoal, platinum-on-charcoal and the like, preferably in an alcoholic medium. The compounds of formula (I) wherein L is methyl or phenylmethyl can be converted into compounds of formula (I) wherein L is a C_{1-6}alkyloxycarbonyl group by reacting the methyl or phenylmethyl derivative with C_{1-6}alkyloxycarbonyl halides such as, for example, ethyl chloroformate in a suitable reaction-inert solvent and in the presence of a base like N,N-diethylethanamine. The compounds of formula (I) wherein L is hydrogen can be obtained from compounds of formula (I) wherein L is phenylmethyl or C_{1-6}alkyloxycarbonyl following art-know

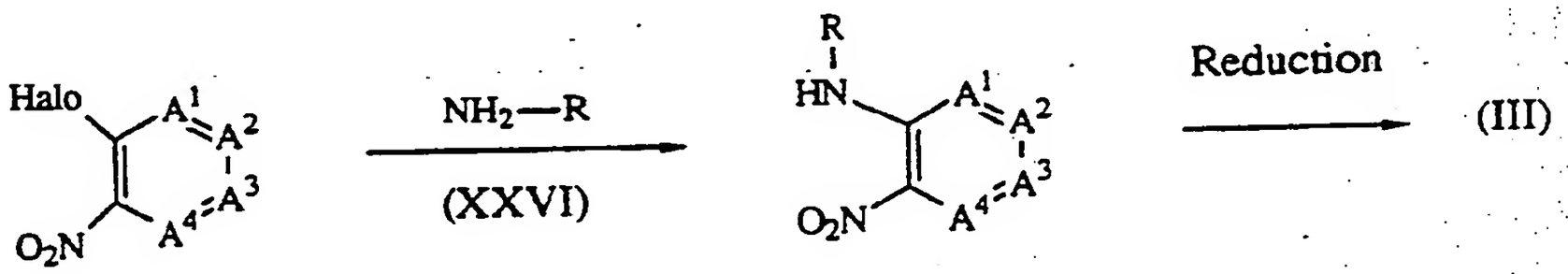
procedures like catalytic hydrogenation or hydrolysis in an acidic or alkaline medium depending on the nature of L.

In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

Some intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and others are new. A number of such preparation methods will be described hereinafter in more detail.

Starting materials such as the intermediates of formulae (II), (IV), (VI), (VIII), (X), (XII), (XIII) and (XV) can conveniently be prepared following procedures similar to those described in for example, US-4,219,559; 4,556,660; 4,634,704; 4,695,569; 4,695,575, 4,588,722, 4,835,161 and 4,897,401 and in EP-A-0,206,415; 0,282,133; 0,297,661 and 0,307,014.

The intermediates of formula (III) can be prepared from an aromatic starting material with vicinal halo and nitro substituents (XXVII) by reaction with a suitable amine of formula (XXVI), followed by art-known nitro-to-amine reduction.



(XXVII)

The intermediates of formulae (V), (VII), (IX) and (XI) then, can be prepared from the intermediates of formula (III) following art-known procedures of converting aromatic products with vicinal amino groups into benzimidazoles, imidazopyridines and/or purines.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. More particularly, they are active antiallergic and antihistaminic compounds which activity can be demonstrated by, e.g., the results obtained in the test "Protection of Rats

from Compound 48/80-induced lethality", the "PCA (passive cutane anaphylaxis)-test in Rats" described in Drug Dev. Res., 5, 137-145 (1985), the "Histamine-induced lethality test in Guinea Pigs" and the "Ascaris Allergy test in Dogs". The latter two tests are described in Arch. Int. Pharmacodyn. Ther. 251, 39-51 (1981).

An interesting feature of the present compounds resides in their rapid onset of action and favorable duration of action.

In view of their antiallergic properties, the compounds of formula (I) and their acid addition salts are very useful in the treatment of broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antiallergic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a

significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt form thereof.

Those of skill in treating allergic diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

Experimental part

A. Preparation of the intermediates

Example 1

To a mixture of 15.5 parts of 2-chloro-1H-benzimidazole and 235 parts of N,N-dimethylacetamide there were added 22 parts of 4-(chloromethyl)-2-methylthiazole monohydrochloride and 25.4 parts of sodium carbonate. The whole was stirred for 18 hours at 75°C and was then poured into water. The product was extracted with

4-methyl-2-pentanone and the extract was washed with water, dried, filtered and evaporated. The residue was crystallized from 2,2'-oxybispropane, yielding 11.3 parts (42.8%) of 2-chloro-1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazole (interm. 1).
In a similar manner there was also prepared 2-chloro-1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazole (interm. 2).

Example 2

a) To a stirred and refluxing mixture of 60 parts of 4-fluorobenzenethiol, 93 parts of 1-bromo-3-chloropropane, 100 parts of ethanol and 45 parts of water there was added dropwise a solution of 19 parts of sodium hydroxide in 80 parts of water. Stirring at reflux temperature was continued for 8 hours. After cooling, the organic layer was separated and distilled under reduced pressure ($1.7\ 10^3$ Pa), yielding two fractions of resp. 53 parts (bp. 136-140°C) and 32 parts (bp. 140-152°C) of product. Total yield : 85 parts of 1-[(3-chloropropyl)thio]-4-fluorobenzene (interm. 3).

b) A mixture of 67.5 parts of intermediate 3; 42.9 parts of 1,4-dioxa-8-azaspiro[4,5]-decane, 47.7 parts of sodium carbonate, a few crystals of potassium iodide and 2400 parts of 4-methyl-2-pentanone was stirred for 70 hours at reflux temperature. The reaction mixture was filtered while hot and the filtrate was washed with 1,1'-oxybis-ethane and evaporated. The residue was triturated in 2,2'-oxybispropane while cooling at -20°C. A first fraction of 4.4 parts of product was obtained by filtration. Evaporation of the mother liquor yielded a second fraction of 97 parts of product. Total yield : 101.4 parts of 1,4-dioxa-8-[3-[(4-fluorophenyl)thio]propyl]-8-azaspiro[4,5]decane; mp. 135.5-140°C (interm. 4)

Example 3

a) A mixture of 2.44 parts of 6-methyl-2-pyridinemethanamine, 3.2 parts of 2-chloro-3-nitropyridine, 1.7 parts of sodium hydrogen carbonate and 120 parts of ethanol was stirred for 3 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth. After cooling, the precipitate which formed in the filtrate was filtered off and dried, yielding 2.5 parts (51%) of 6-methyl-N-(3-nitro-2-pyridinyl)-2-pyridinemethanamine; mp. 131.7°C (interm. 5).

b) A mixture of 55 parts of intermediate 5; 2 parts of a solution of thiophene in methanol 4% and 480 parts of methanol was hydrogenated at normal pressure and at 50°C with 3 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated, yielding 47 parts (99.7%) of N^2-[(6-methyl-2-pyridinyl)-methyl]-2,3-pyridinediamine (interm. 6).

c) A mixture of 47 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 47 parts of intermediate 6 and 900 parts of tetrahydrofuran was stirred overnight at room temperature. There was added 2,2'-oxybispropane to enhance crystallization. The product was filtered off and dried, yielding 78.5 parts (83.5%) of ethyl 4-[[[[2-[[(6-methyl-2-pyridinyl)methyl]amino]-3-pyridinyl]amino]thioxomethyl]amino]-1-piperidinecarboxylate; mp. 176°C (interm. 7).

B. Preparation of the final compounds

Example 4

To a stirred mixture of 45 parts of 2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-benzimidazole and 376 parts of N,N-dimethylformamide there were added portionwise 12.2 parts of a dispersion of sodium hydride in mineral oil (60%) and, after stirring for 1/2 hour, a solution of 28 parts of 2-(chloromethyl)-6-methylpyridine monohydrochloride in some N,N-dimethylformamide. Stirring at room temperature was continued overnight. After the addition of ethanol, the reaction mixture was poured into water. The product was extracted with methylbenzene and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:5/2) salt in acetonitrile. The product was filtered off and dried, yielding 27.8 parts (29.2%) of 1-[(6-methyl-2-pyridinyl)methyl]-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-benzimidazole ethanedioate (1:5/2); mp. 155.3°C (comp. 48).

Example 5

To a stirred mixture of 36.7 parts of compound 48 and 267 parts of tetrahydrofuran there were added 15.68 parts of ethyl chloroformate. Stirring was continued for 6 hours and then there were added 11.7 parts of N,N-diethylethanamine. After stirring over weekend, the reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 15.65 parts (44.3%) of ethyl 4-[[1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-yl]-methyl]-1-piperidinecarboxylate; mp. 159.7°C (comp. 53).

Example 6

A mixture of 2.9 parts of ethyl 4-[(1H-benzimidazol-2-yl)amino]-1-piperidinecarboxylate, 1.8 parts of 4-(chloromethyl)-2-methylthiazole monohydrochloride, 2.12 parts of sodium carbonate and 45 parts of N,N-dimethylacetamide was stirred overnight at 70°C. The reaction mixture was poured into water and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.5 parts (37.5%) of ethyl 4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]-amino]-1-piperidinecarboxylate; mp. 160°C (comp. 12).

Example 7

A mixture of 25 parts of compound 12; 34 parts of potassium hydroxide and 160 parts of 2-propanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was converted into the trihydrochloride salt in 2-propanol. The product was filtered off and dried, yielding 20 parts (71.2%) of 1-[(2-methyl-4-thiazolyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine trihydrochloride hemihydrate; mp. 206.4°C (comp. 13).

Example 8

A mixture of 15 parts of compound 58 and 224 parts of hydrobromic acid 48% was refluxed for 3 hours. The reaction mixture was evaporated and the residue was taken up in water. After basifying with sodium hydroxide solution, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from acetonitrile, yielding 5 parts (41.3%) of 1-[(4-methyl-2-thiazolyl)-methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine (comp. 59).

Example 9

A mixture of 2.3 parts of 6-(2-chloroethyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one, 3.3 parts of compound 13; 1.6 parts of sodium carbonate and 160 parts of 4-methyl-2-pentanone was stirred for 48 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.64 parts (31.6%) of

7-methyl-6-[2-[4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 129.8°C (comp. 18).

Example 10

A mixture of 2.26 parts of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 3.2 parts of compound 2; 1.06 parts of sodium carbonate and 45 parts of N,N-dimethylacetamide was stirred overnight at 70°C. The reaction mixture was poured into water. The precipitate was filtered off and boiled in methanol. The product was filtered off while hot, yielding 2.1 parts (41.5%) of 2-methyl-3-[2-[4-[[3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinyl]ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 233.1°C (comp. 7).

Example 11

The following reaction was carried out under a nitrogen atmosphere. To a mixture of 7.5 parts of ethyl 4-hydroxy-1-piperidinecarboxylate and 94 parts of N,N-dimethylformamide there were added portionwise 2.1 parts of a dispersion of sodium hydride in mineral oil (50%). After stirring for 1 hour at room temperature and for 20 min at 40°C, there was added dropwise a solution of 11.3 parts of intermediate 1 in 94 parts of N,N-dimethylformamide. Stirring was continued overnight at room temperature. After addition of some ethanol, the reaction mixture was evaporated. The residue was poured into ice-water and the whole was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated, yielding 13 parts (75.5%) of ethyl 4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]-oxy]-1-piperidinecarboxylate (comp. 20).

Example 12

A mixture of 4.5 parts of compound 13; 2 parts of polyoxymethylene, 5 parts of potassium acetate and 120 parts of methanol was hydrogenated at normal pressure and at 50°C with 1 part of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was taken up in water. After basifying with sodium carbonate, the product was extracted with trichloromethane. The extract was dried, filtered and evaporated and the residue was converted into the ethanedioate (1:2) salt in methanol. The product was filtered off and dried, yielding 3.7 parts (70.9%) of N-(1-methyl-4-piperidinyl)-1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-amine ethanedioate (1:2); mp. 221.3°C (comp. 16).

Example 13

A mixture of 78 parts of intermediate 7; 58.5 parts of mercury(II)oxide, 1 part of sulfur and 800 parts of ethanol was stirred for 2 hours at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated, yielding 63.5 parts (88.5%) of ethyl 4-[[3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl]amino]-1-piperidinecarboxylate (comp. 1).

Example 14

Trough a stirred mixture of 3.23 parts of compound 2 and 80 parts of methanol there were bubled 0.9 parts of oxirane. Stirring was continued overnight at room temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / CH_3OH 96:4). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.7 parts (19%) of 4-[[3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl]amino]-1-piperidineethanol; mp. 152.0°C (comp. 4).

Example 15

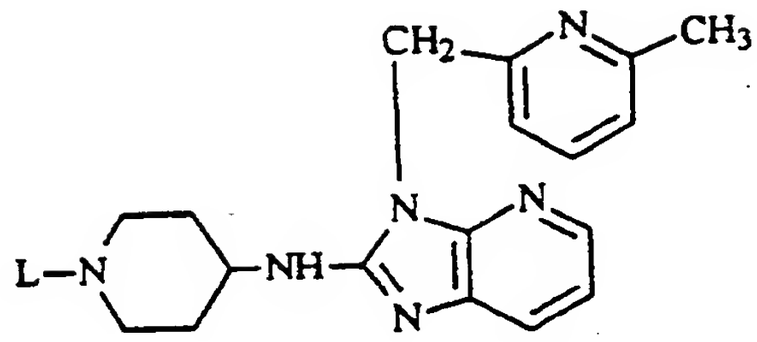
A mixture of 9 parts of compound 5; 11 parts of potassium hydroxide and 120 parts of 2-propanol was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane (2x) and the combined extracts were dried, filtered and evaporated, yielding 7.5 parts (100%) of N-[1-(2-aminoethyl)-4-piperidinyl]-3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (comp. 8).

Example 16

A mixture of 1.2 parts of 2-chloropyrimidine, 3.7 parts of compound 8; 0.9 parts of sodium hydrogen carbonate and 80 parts of ethanol was stirred overnight at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was crystallized from a mixture of acetonitrile and methanol. The product was filtered off and dried in vacuo at 130°C overnight, yielding 1 part (22.5%) of 3-[(6-methyl-2-pyridinyl)methyl]-N-[1-[2-[(2-pyrimidinyl)amino]-ethyl]-4-piperidinyl]-3H-imidazo[4,5-b]pyridin-2-amine; mp. 187.4°C (comp. 9).

All compounds listed in tables 1, 2, 3, 4 and 5 were prepared following methods of preparation described in examples 4 - 16, as is indicated in column 2 (Ex. No.)

Table 1



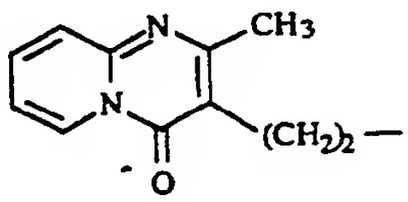
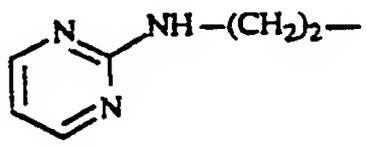
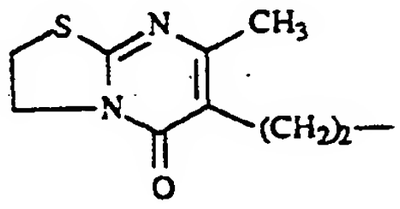
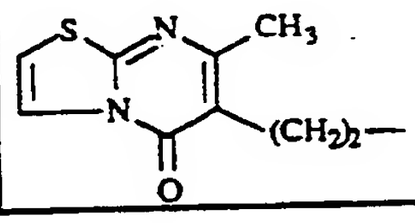
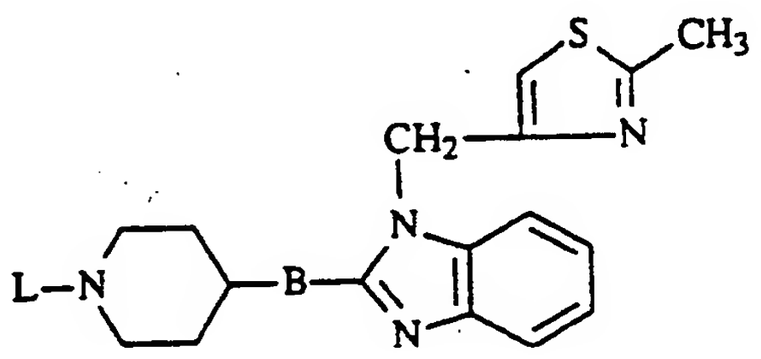
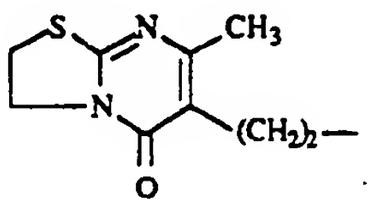
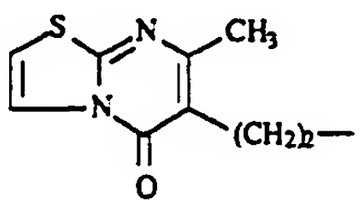
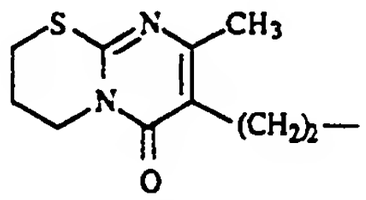
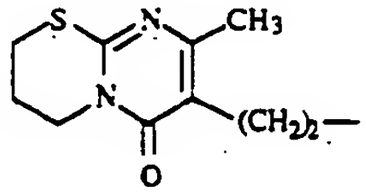
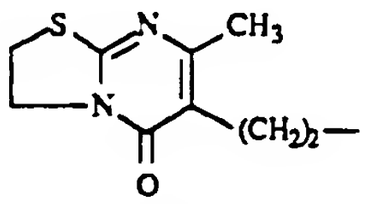
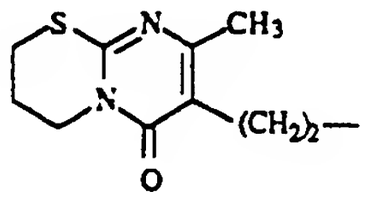
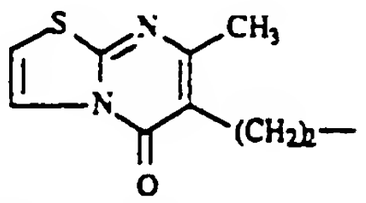
Comp. No.	Ex. No.	L	Physical data
1	13	CH_3-CH_2-OOC-	-
2	7	H-	147.6°C / H_2O(1:1/2)
3	12	CH_3-	130.5°C
4	14	HO-$(CH_2)_2$-	152.0°C
5	10	CH_3-CH_2-OOC-NH-$(CH_2)_2$-	139.6°C
6	10	CH_3O-C_6H_4-$(CH_2)_2$-	142.3°C
7	10		233.1°C
8	15	NH_2-CH_2-CH_2-	-
9	16		187.4°C
10	9		185.4°C
11	9		215.5°C

Table 2



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
12	6	CH_3-CH_2-OOC-	NH	160°C
13	7	H	NH	206.4°C/HCl (1:3)/H_2O (1:1/2)
14	10	CH_3-CH_2-O-$(CH_2)_2$-	NH	201.6°C/$(COOH)_2$ (1:2)
15	10	CH_3O-C_6H_4-$(CH_2)_2$-	NH	228.5°C/HCl (1:2)/H_2O
16	12	CH_3-	NH	221.3°C/$(COOH)_2$ (1:2)
17	9		NH	185.4°C
18	9		NH	129.8°C
19	9		NH	186.1°C
20	11	CH_3-CH_2-OOC-	O	-
21	7	H	O	127.7°C
22	9		O	137.0°C
23	9		O	160.4°C
24	4	C_6H_5-CH_2-	CH_2	115.1°C
25	5	CH_3-CH_2-OOC-	CH_2	125.0°C
26	7	H	CH_2	155.9°C
27	9		CH_2	150.7°C (E)-2-butenedioate (1:3/2) 2-propanolate(1:1)
28	9		CH_2	153.4°C

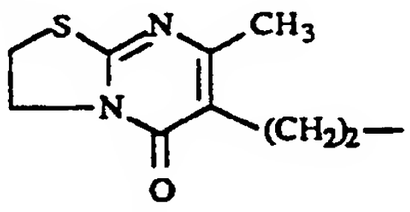
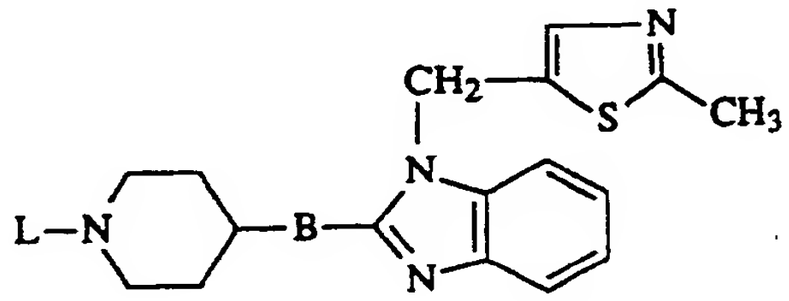
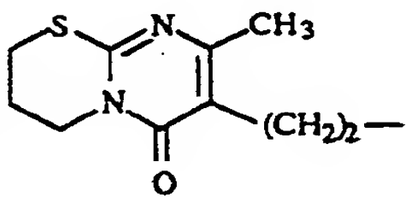
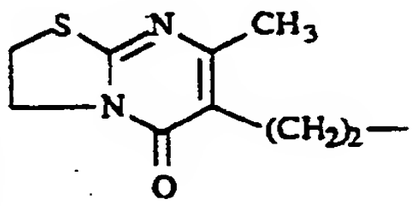
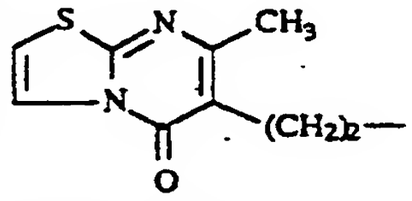
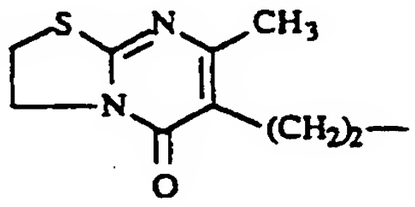
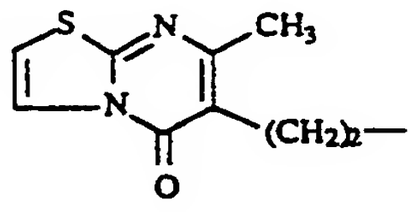
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
29	9		CH_2	179.9°C

Table 3



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
30	6	CH_3-CH_2-OOC-	NH	155.1°C
31	7	H-	NH	239.2°C
32	9		NH	196.7°C
33	9		NH	204.2°C
34	9		NH	125.5°C
35	4	C_6H_5-CH_2-	CH_2	119.6°C
36	5	CH_3-CH_2-OOC-	CH_2	101.3°C
37	7	H-	CH_2	-
38	9		CH_2	161.7°C / H_2O (1:1/2)
39	9		CH_2	158.5°C / H_2O (1:3/2)

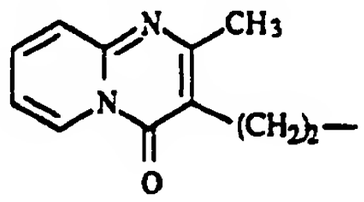
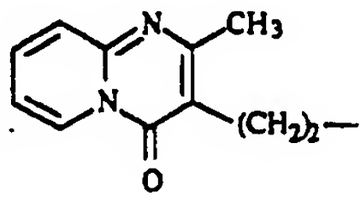
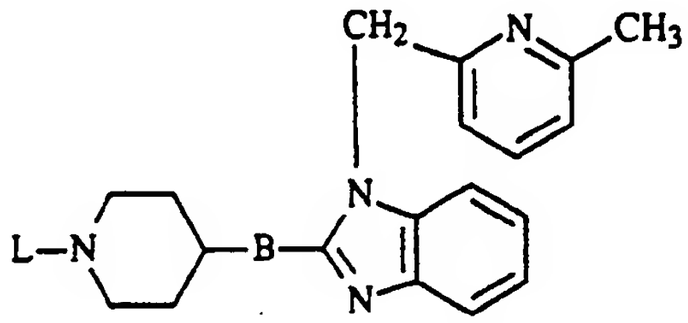
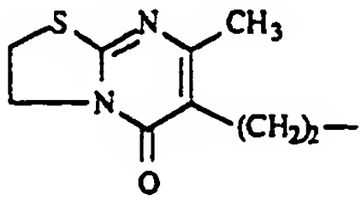
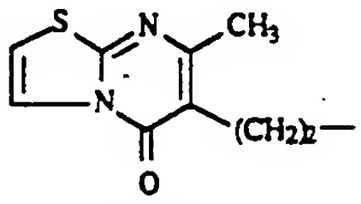
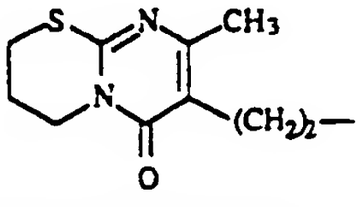
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
40	9		CH_2	171.0°C
41	9		NH	219.8°C
42	12	H_3C-	NH	114.6°C/H_2O (1:3/2)
43	9	CH_3O-C_6H_4-$(CH_2)_2$-	NH	103.1C

Table 4



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
44	6	CH_3-CH_2-OOC-	NH	182.6°C
45	7	H	NH	161.0°C/H_2O (1:1/2)
46	9		NH	206.6°C
47	9		NH	225.3°C
48	4	C_6H_5-CH_2-	CH_2	155.3°C/$(COOH)_2$ (1:5/2)
49	9		NH	131.9°C / H_2O
50	11	CH_3-CH_2-OOC-	O	-
51	7	H	O	106.9°C

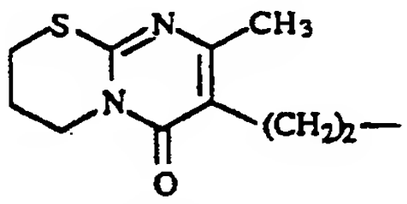
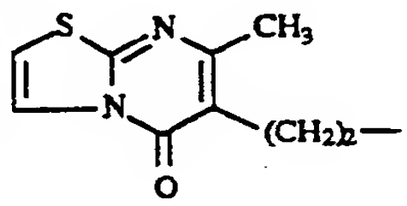
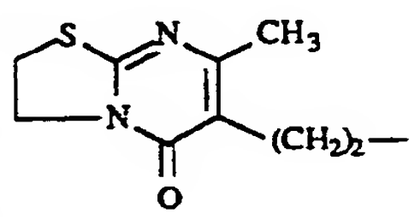
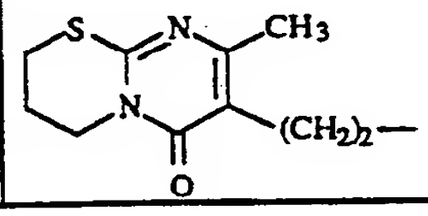
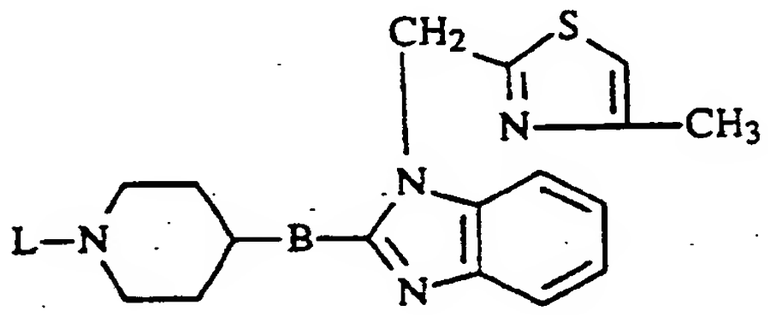
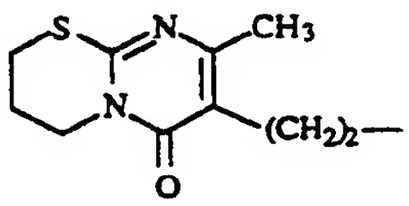
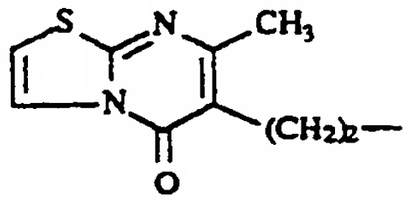
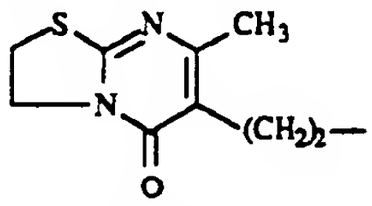
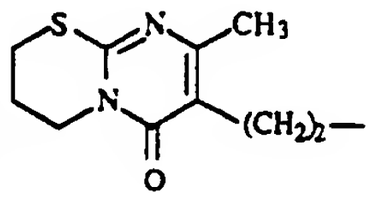
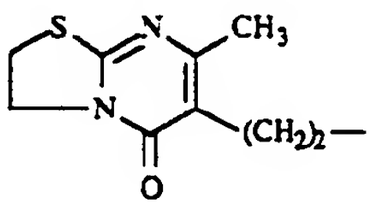
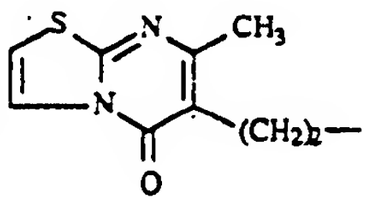
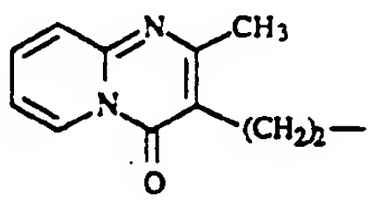
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
52	9		O	144.0°C
53	5	CH_3-CH_2-OOC-	CH_2	159.7°C
54	7	H	CH_2	-
55	9		CH_2	176.1°C
56	9		CH_2	222.5°C (E)-2-butenedioate(1:1)
57	9		CH_2	160.6°C (E)-2-butenedioate(1:3/2) 2-propanolate(1:1)

Table 5



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
58	6	CH_3-CH_2-OOC-	NH	183.6°C
59	8	H-	NH	-
60	9		NH	147.7°C / H_2O
61	9		NH	215.5°C
62	12	CH_3-	NH	128.5°C/H_2O (1:1/2)

Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
63	9		NH	196.7°C
64	9	CH_3O-C_6H_4-$(CH_2)_2$-	NH	109.9°C
65	4	C_6H_5-CH_2-	CH_2	129.5°C
66	5	CH_3-CH_2-OOC-	CH_2	-
67	7	H-	CH_2	-
68	9		CH_2	126.6°C
69	9		CH_2	170.4°C
70	9		CH_2	176.9°C (Z)-2-butenedioate(1:2)
71	9		CH_2	158.8°C

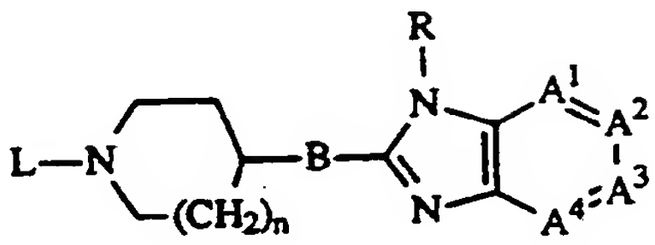
C. Pharmacological example

Example 17

The useful anti-allergic and anti-histaminic properties of the compounds of formula (I) can be demonstrated, e.g., in the test "Protection of rats from compound 48/80 - induced lethality" which is described in US-4,556,660. The compounds of formula (I) were administered subcutaneously and/or orally to rats. The ED_{50}-value (mg/kg) for the compounds 9, 16, 19, 23, 27, 28, 29, 55, 62, 69 and 70 was found to be 0.04 mg/kg.

Claims

1. A compound having the formula :



(I),

a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

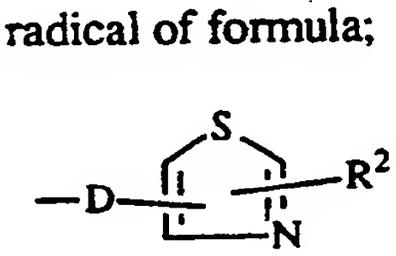
$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=CH-CH=CH- (a-1),
-N=CH-CH=CH- (a-2),
-CH=N-CH=CH- (a-3),
-CH=CH-N=CH- (a-4),
-CH=CH-CH=N- (a-5),
-N=CH-N=CH- (a-6) or
-CH=N-CH=N- (a-7);

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy or trifluoromethyl;

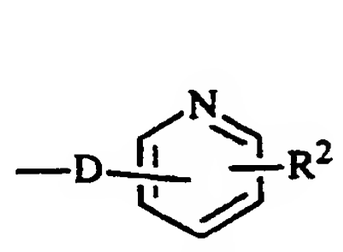
B represents NR^1, CH_2, O, S, SO or SO_2 wherein R^1 is hydrogen or C_{1-4}alkyl;

R is a radical of formula;



(b-1)

or



(b-2)

;

wherein D is C_{1-4}alkanediyl;

R^2 is C_{1-6}alkyl;

n is 0, 1 or 2 ;

L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; or a radical of formula

-Alk-R^3 (c-1);

-Alk-Y-R^4 (c-2);

-Alk-Z^1-C(=X)-Z^2-R^5 (c-3); or

-CH_2-CHOH-CH_2-O-R^6 (c-4); wherein

R^3 is cyano, aryl or Het;

R^4 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^5 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^6 is aryl or naphthalenyl;

Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;

Z^1 and Z^2 each independently are O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;

X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;

each Alk independently is C_{1-6}alkanediyl;

each Het is :

(i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;

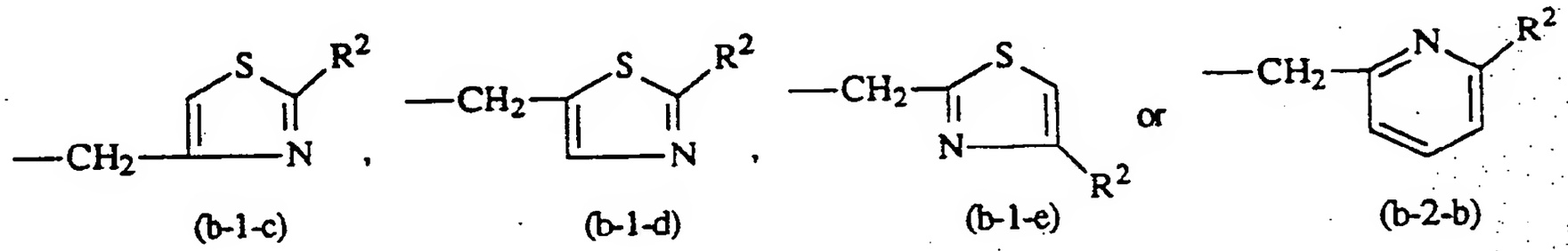
(ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or

(iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;

wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy, mercapto, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxy, aryl, arylC_{1-6}alkyl, carboxyl, C_{1-6}alkylaminocarbonylamino, arylaminocarbonylamino, oxo or thio; and

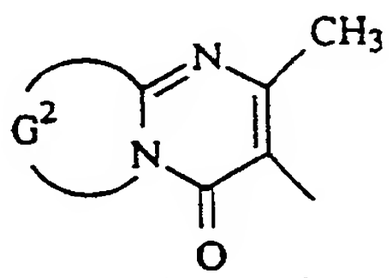
each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl.

2. A compound according to claim 1 wherein $-A^1=A^2-A^3=A^4-$ represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH_2 or O; R represents a radical of formula



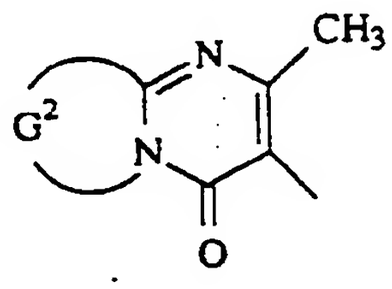
(b-1-c) (b-1-d) (b-1-e) (b-2-b)

R^2 represents C_{1-4}alkyl; n is 1; L represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{1-4}alkanediyl; R^3 represents phenyl, C_{1-4}alkyloxyphenyl or a radical of formula



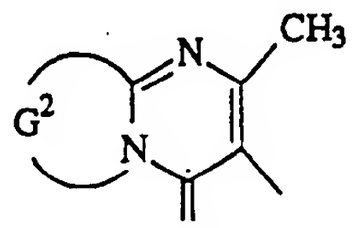
wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-; Y represents O or NH; R^4 represents hydrogen, C_{1-4}alkyl or pyrimidinyl; R^5 represents C_{1-4}alkyl; Z^1 represents NH; Z^2 represents O; and X represents O.

3. A compound according to claim 1 wherein B represents NH or CH_2; R^2 represents methyl; L represents C_{1-4}alkyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{2-4}alkanediyl; R^3 represents 4-methoxyphenyl or a radical of formula



wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$-, -S-CH=CH-; Y represents O or NH; R^4 represents C_{1-4}alkyl or 2-pyrimidinyl.

4. A compound according to claim 1 wherein L represents methyl or a radical of formula -Alk-R^3 (c-1), Alk represents 1,2-ethanediyl and R^3 represents 4-methoxyphenyl or a radical of formula



wherein G^2 represents CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-.

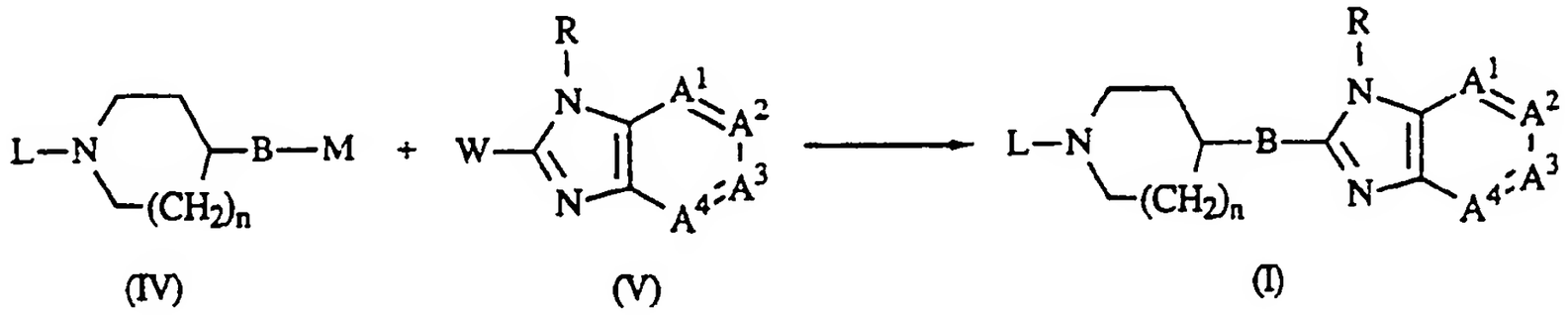
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an effective antiallergic amount of a compound as claimed in claim 1.

6. A process for preparing a pharmaceutical composition as claimed in claim 5, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.

7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

8. A process of preparing a compound as claimed in claim 1, characterized by

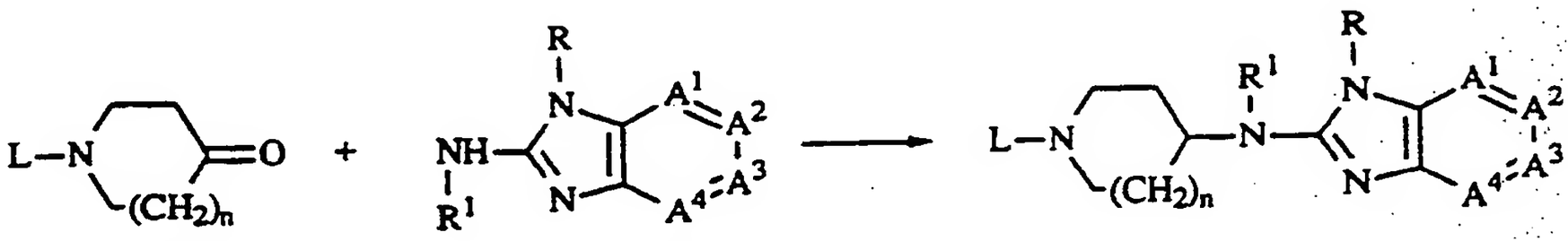
a) reacting a piperidine of formula (IV) wherein M represents hydrogen when B is other than hydrogen, or wherein M represents an alkali or earth alkaline metal when B represents CH_2, with a reagent of formula (V) wherein W represents a reactive leaving group,



(IV) (V) (I)

in a reaction-inert solvent, optionally in the presence of a base;

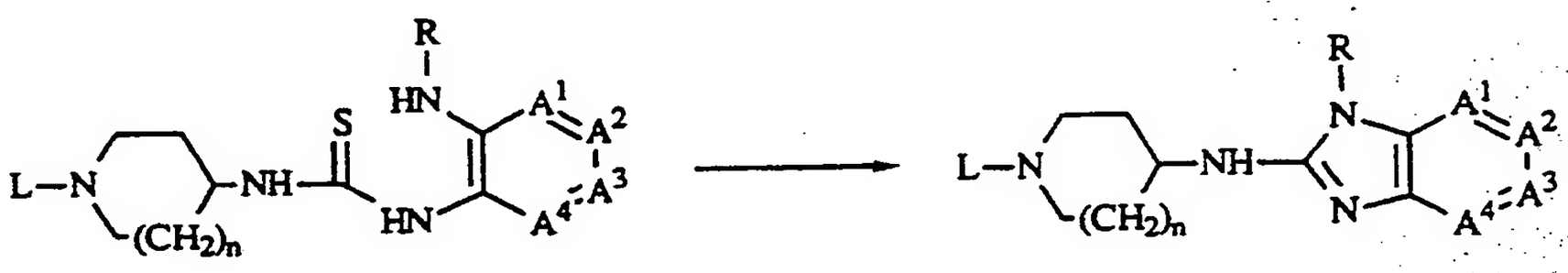
b) reductively N-alkylating a 4-piperidinone derivative of formula (XII) with an amine of formula (VII-a),



(XII) (VII-a) (I-b)

in the presence of an appropriate reductant in a reaction-inert solvent, thus yielding a compound of formula (I-b);

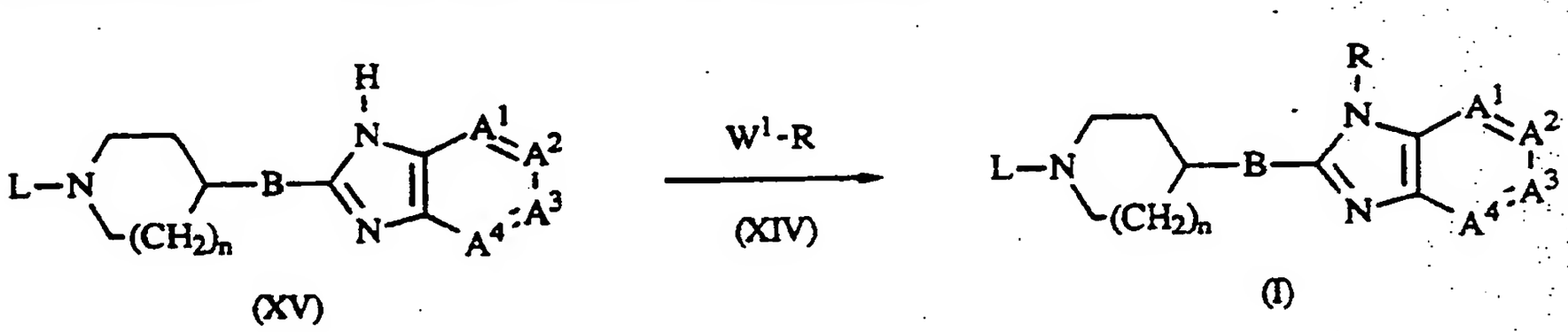
c) cyclodesulfurizing a thiourea of formula (II-a-1),



(II-a-1) (I-b-1)

by reaction with a metal oxide or salt in a reaction-inert solvent, optionally in the presence of a small amount of sulfur;

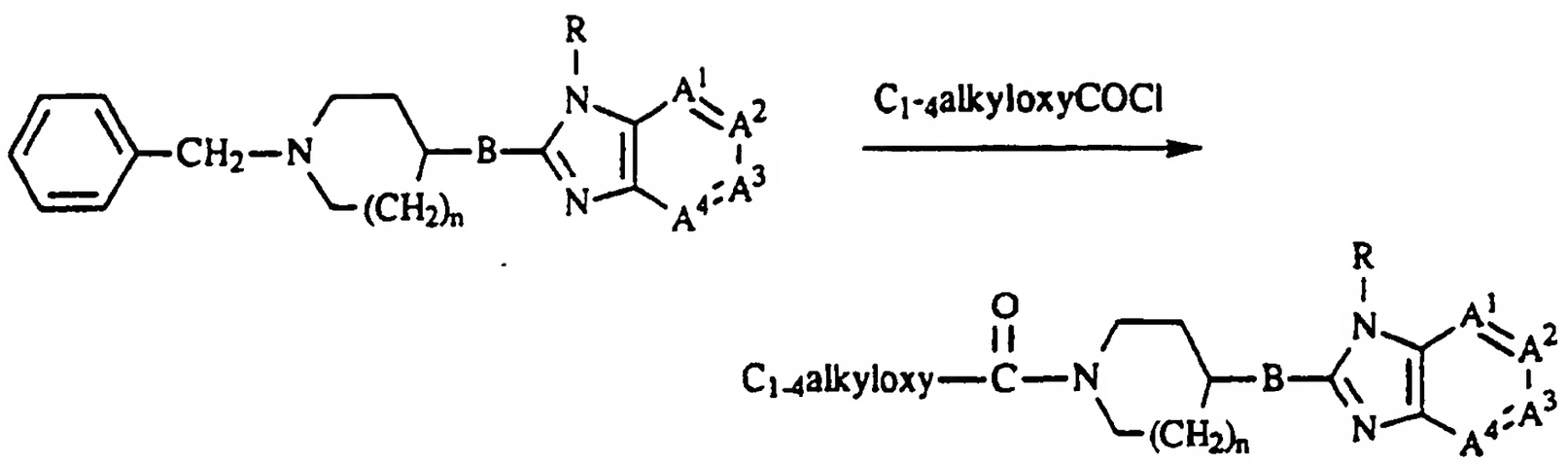
d) N-alkylating an intermediate of formula (XV) with an alkylating reagent of formula (XIV) wherein W represents a reactive leaving group,



(XV) (XIV) (I)

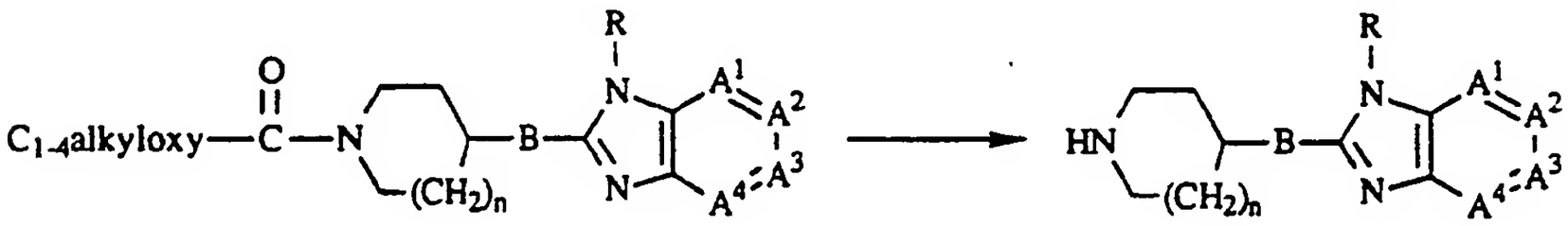
in a reaction-inert solvent in the presence of a base and at an elevated temperature;

e) converting a compound of formula (I) wherein L represents benzyl into a compound wherein L represents C_{1-4}alkyloxycarbonyl,



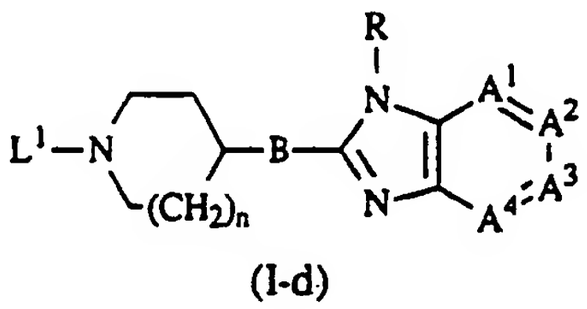
by reaction with a C_{1-4}alkylchloroformate in the presence of a base in a reaction-inert solvent;

f) hydrolyzing a compound of formula (I) wherein L represents C_{1-4}alkyloxy-carbonyl in an aqueous acidic or basic medium to a compound of formula (I-e),



(I-e)

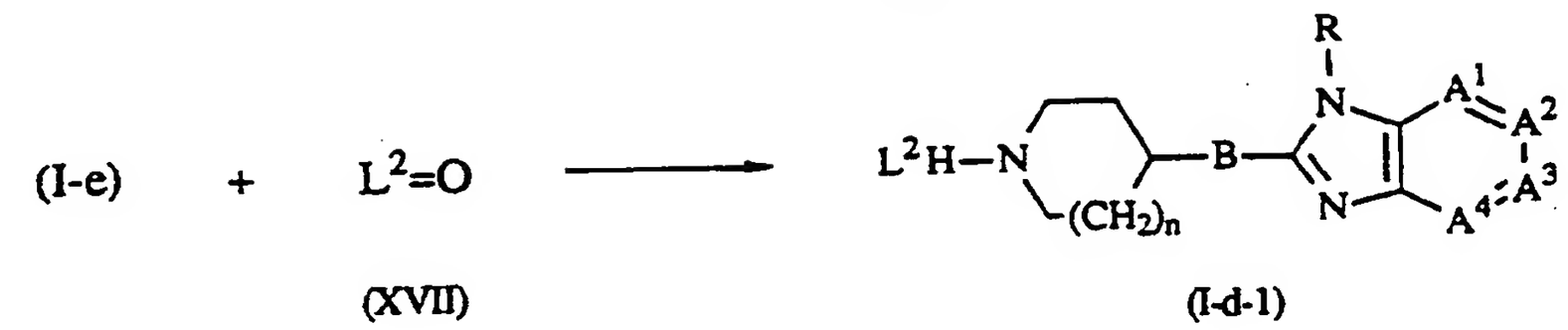
g) N-alkylating a compound of formula (I-e) with an alkylating reagent of formula L^1-W^1 (XVI) in a reaction-inert solvent in the presence of a base, thus preparing a compound of formula



(I-d)

h) reductively N-alkylating a compound of formula (I) with an aldehyde or ketone of formula L^2=O (XVII) wherein L^2 represents a geminal bivalent radical comprising C_{3-6}cycloalkylidene, C_{1-12}alkylidene, R^3-C_{1-6}alkylidene, R^4-Y-C_{1-6}alkylidene or R^5-Z^2-C(=X)-Z^1-C_{1-6}alkylidene,

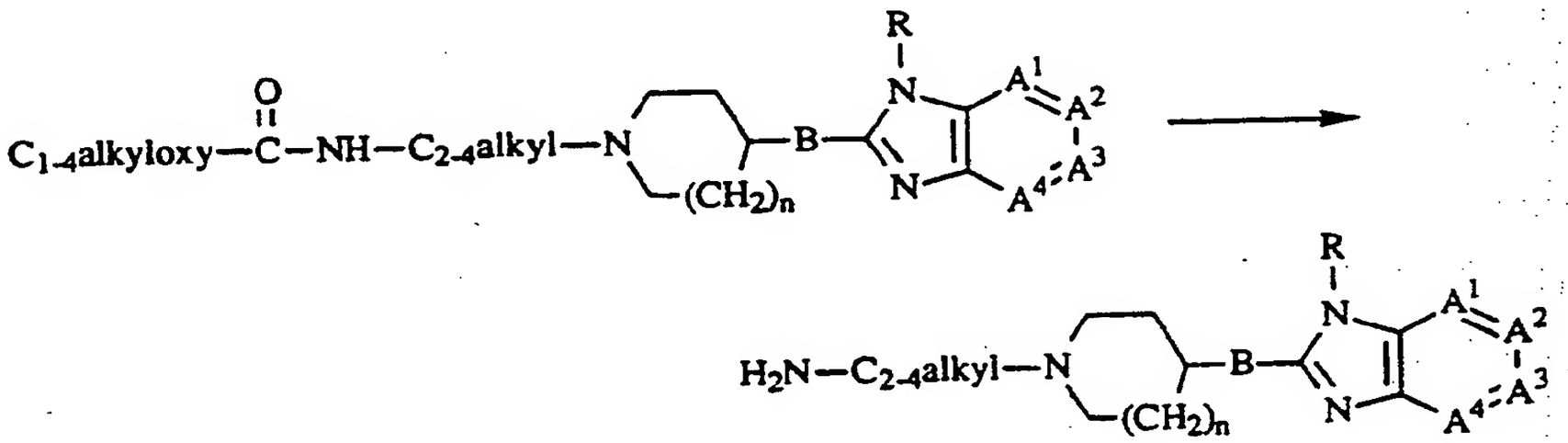
40



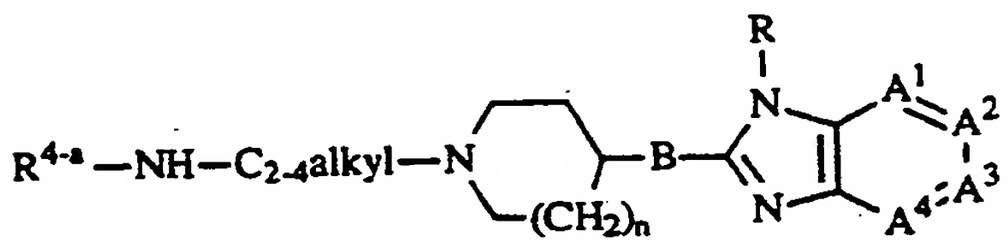
(I-e) + L^2=O (XVII) → (I-d-1)

in a reaction-inert sovent in the presence of a reductant;

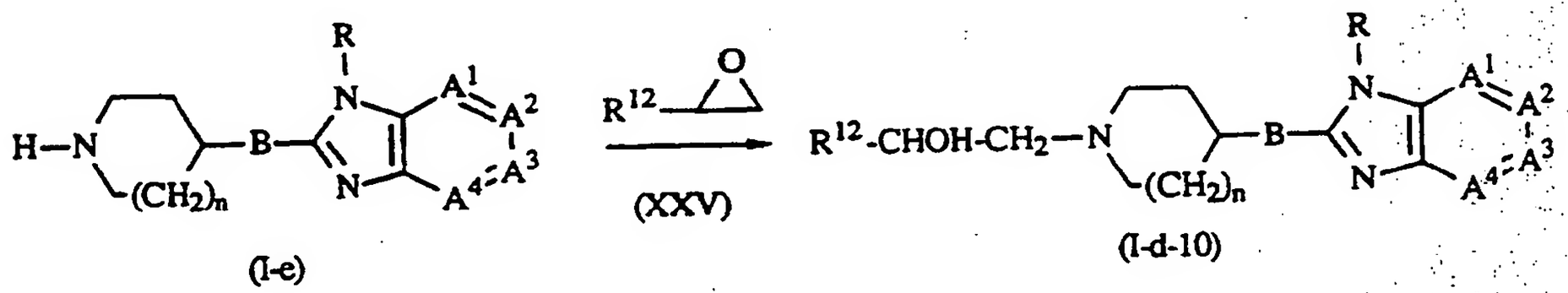
i) hydrolyzing a compound of formula (I) wherein L represents C_{1-4}alkyloxy-carbonylaminoC_{2-4}alkyl in a basic aqueous medium thus yielding a compound wherein L represents an aminoC_{2-4}alkyl radical,



j) alkylating the thus obtained compound wherein L represents aminoC_{2-4}alkyl with a reagent of formula R^{4-a}-W^1 wherein R^{4-a} represents aryl or Het and W^1 represents a reactive leaving group thus yielding a compound of formula



k) reacting a compound of formula (I-e) with an epoxide of formula (XXV) wherein R^{12} represents hydrogen, C_{1-4}alkyl or R^6-O-CH_2-,



(I-e) (XXV) (I-d-10)

in a reaction-inert solvent; and, if desired, converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or conversely, converting the salt form into the free base by treatment with alkali; and/or preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Applic. .i No PCT/EP 91/01292

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 513/04 C 07 D 401/14 C 07 D 401/04
C 07 D 519/00 C 07 D 473/40 A 61 K 31/505 A 61 K 31/425
C 07 D 417/14, C 07 D 471/04, C 07 D 473/00, C 07 D 473/30, A 61 K 31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0297661 (JANSSEN PHARMACEUTICA NV) 4 January 1989, see the whole document (cited in the application)	1-8
X	EP,A,0206415 (JANSSEN PHARMACEUTICA NV) 30 December 1986, see the whole document (cited in the application)	1-8
X	US,A,4897401 (JANSSEN PHARMACEUTICA NV) 30 January 1990, see the whole document (cited in the application)	1-8
X	US,A,4835161 (JANSSEN PHARMACEUTICA NV) 30 May 1989, see the whole document (cited in the application)	1-8

-/-

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance.

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07-10-1991	19 NOV 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,4634704 (JANSSEN PHARMACEUTICA NV) 6 January 1987, see the whole document (cited in the application) ---	1-8
X	EP,A,4556660 (JANSSEN PHARMACEUTICA NV) 3 December 1985, see the whole document (cited in the application) ---	1-8
X	US,A,4588722 (JANSSEN PHARMACEUTICA NV) 13 May 1986, see the whole document (cited in the application) ---	1-8
X	US,A,4695569 (JANSSEN PHARMACEUTICA NV) 22 September 1987, see the whole document (cited in the application) ---	1-8
X	EP,A,4695575 (JANSSEN PHARMACEUTICA NV) 22 September 1987, see the whole document (cited in the application) -----	1-8

FURTHER INFORMATION C NTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim numbers * because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

* Claims searched incompletely: 1-8
As the drafting of the claims is not clear and concise (Art. 6 PCT) and encompasses such an enormous amount of products, a complet search is not possible on economic grounds (Art 17(2)(a)(ii), PCT). So the search has been based on the examples

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101292 SA 49002

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0297661	04-01-89	AU-B-	603684	22-11-90
		AU-A-	1835388	05-01-89
		JP-A-	1034979	06-02-89
		US-A-	4988689	29-01-91
EP-A- 0206415	30-12-86	AU-B-	588890	28-09-89
		AU-A-	5919186	08-01-87
		CA-A-	1267889	17-04-90
		JP-A-	62000487	06-01-87
		SU-A-	1581221	23-07-90
		US-A-	5041448	20-08-91
US-A- 4897401	30-01-90	US-A-	5006527	09-04-91
		AU-B-	600144	02-08-90
		AU-A-	1810988	22-12-88
		EP-A-	0295742	21-12-88
		JP-A-	1025776	27-01-89
		SU-A-	1644717	23-04-91
US-A- 4835161	30-05-89	AU-B-	583706	04-05-89
		AU-A-	6821887	06-08-87
		EP-A-	0232937	19-08-87
		JP-A-	62215575	22-09-87
US-A- 4634704	06-01-87	AU-B-	565884	01-10-87
		AU-A-	3387284	18-04-85
		CA-A-	1247614	27-12-88
		EP-A,B	0145037	19-06-85
		JP-A-	61010577	18-01-86
		SU-A-	1440346	23-11-88
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